Summary

Federal-State Toxicology and Risk Analysis Committee Meeting

October 17–19, 2007
Durham, North Carolina

"Safe and Clean Water"

Introduction, Welcome, and Open Remarks for Days 2 and 3: October 18 and 19, 2007

INTRODUCTION

The Federal-State Toxicology and Risk Assessment Analysis Committee (FSTRAC) met October 17–19, 2007, in Durham, North Carolina. The first day of the FSTRAC Meeting was held in conjunction with the 2007 International Society of Exposure Analysis Conference. Representatives from nine states, Canada, and U.S. Environmental Protection Agency (EPA) headquarters, regions, and other offices attended the meeting.

Dr. Ambika Bathija of EPA's Office of Water kicked off the second day of the meeting by asking the attendees to introduce themselves by stating their names and affiliations. She welcomed everyone to the meeting and then introduced Dr. Edward Ohanian, Division Director of EPA's Office of Science and Technology (OST), Health and Ecological Criteria Division (HECD). Dr. Bathija noted that Dr. Ohanian's welcome would be followed by a few words from her Branch Chief, Elizabeth Doyle, and Bill Russo of RTP (Research Triangle Park). Dr. Ohanian welcomed the meeting participants.

WELCOME

Dr. Ohanian apologized for not being with everybody at RTP for the FSTRAC meeting but added that a number of people from his division were attending the meeting. He noted that he was following his doctor's orders that he not travel while recuperating from his accident in July. He noted that his recovery is going very well, and he thanked everyone for the well wishes he had received.

Dr. Ohanian stated that FSTRAC is 22 years old. It was launched in March 1985, and it is really impressive that it has been around for 22 years. He said that he had heard that the ISEA-FSTRAC coordinated meeting had been very productive and that a number of very important emerging issues dealing with exposure assessments and relative source contribution had been addressed. He thanked Bruce Mintz, Pam Shubat, Helen Goeden, Bob Howd, Perry Cohn, Gloria Post, and Ambika Bathija for setting up this particular session. He also thanked Bill Russo and Bruce Mintz for gathering a number of very impressive speakers that would participate for the next 2 days. Dr. Ohanian had heard that Dr. Abdel Kadry would be in the audience and added that therefore everybody would have a chance to ask Dr. Kadry everything they wanted to know about IRIS but were afraid to ask. Dr. Ohanian wished everyone a good and productive meeting and turned the meeting back over to Dr. Bathija.

Dr. Bathija thanked Dr. Ohanian and introduced Dr. Elizabeth Doyle, Branch Chief of EPA's Human Health Risk Assessment Branch.

Dr. Doyle began by welcoming everyone. She said that she was eager to find out what is going on in the states and that she would let everyone know where EPA is. She commented that her branch has had a long absence from working on exposure assessment so they've taken steps to try to move the process forward. A lot of the comments yesterday were right on target with what EPA has been thinking about. EPA was happy to hear them, she noted, "because it gives us the sense that we are moving in the direction that the community would like to see."

Dr. Doyle introduced Tina Moore, who is new to their office. Tina came on board Monday, and she has an epidemiology background. She has come in to work on EPA's exposure assessment process. Dr. Doyle said that Tina and she would be happy to have any input from participants on

the direction they'd like to go because EPA wants to move forward in the process of exposure assessment. Considering RSC also is certainly high on EPA's list. Dr. Doyle added that people should feel free to contact Tina, Ed, or her.

Dr. Doyle noted that a number of the chemicals on the agenda are the ones that they are working on actively. She mentioned that they have a great interest in PBDEs, as well as microbial risk assessment. She stated that she would welcome the audience's interest in microbial risk assessment development. She noted that EPA is also working on criteria development for recreational waters—how to develop 304(a) criteria to update EPA's 1986 guidelines. Dr. Alfred Dufour of EPA's National Exposure Research Laboratory in RTP is actively involved with that, and he is a great help to EPA. EPA is also looking to the future, possibly for pathogens of concern and how to deal with them. At this point EPA is still addressing its process with indicators.

Dr. Doyle mentioned that this meeting would provide an opportunity for EPA to hear from the participants officially or unofficially. EPA welcomes that. EPA would like to know what people see as emerging issues, where they have particular areas of concern, where EPA can be helpful, and where EPA needs to focus more attention. She added, "Even if you just have questions because EPA is doing something that makes no sense to you, by all means take the opportunity to talk to us or call later." Dr. Doyle thanked everyone for coming to the meeting and turned the meeting back over to Dr. Bathija.

Dr. Bathija thanked Dr. Doyle and introduced Bill Russo to welcome the participants and give an overview of the ORD/NHEERL lab.

Mr. Russo welcomed everyone to Durham and the RTP area, noting that it is the location where the Office of Research and Development has some of its major research laboratories. He said, "I hope you take advantage of the opportunity, as our scientists come down and present, to talk with them about their activities and to make some contacts that you can follow up on." He noted that he would provide a brief overview of ORD and move right into his introductory presentation on the NHEERL research program.

The following topics were discussed during the 3-day meeting:

- NHANES 1999-2008: Health and Environmental Data
- Water Intake Collection in National Federal Dietary Surveys
- Incidental Water Ingestion During Recreational Swimming
- Drinking Water Intake by Infants Living in Rural Quebec
- Revisions to the Exposure Factors Handbook and Available Drinking Water Data
- Infant Drinking Water Intake Rates for Risk Assessment
- Examination of Drinking Water Survey Data
- Use of Multiple Intake Rates in the Derivation of Groundwater Standards
- Characterizing Exposures to Arsenic and Co-occurring Contaminants Using the Modeling Environment for Total Risk Studies (MENTOR)
- Exposure to Arsenic; Everything But the Kitchen Sink
- Manganese: A Case Study for Children's Health
- Modeling Direct and Indirect Water Ingestion Exposure to Pesticides
- Water and Food Modeling Used with a Margin of Exposure for Pesticides Registration Decisions
- Overview of Research on Multipathway Exposures to Volatile Chemicals in Tap Water

- Characterizing Total Indoor Water Exposures to Volatile DBPs Using the Total Exposure Model (TEM)
- Physiological Modeling of Multiroute Exposure to Volatile Drinking Water Contaminants
- Exposure Assessment Methods for Ambient Water Quality Criteria
- Multiple Source Exposure (RSC) Approach Applied to Chloroform
- Overview of ORD/NHEERL & NERL
- U.S. EPA's Integrated Risk Information System (IRIS): An Update on the Program
- Current Research and Testing Activities in the National Toxicology Program
- OST/HECD/OW Update
- Overview of ATSDR Activities for PFOA
- Perfluorinated Chemicals: Overview of EPA's Research Activities
- Immediate and Long-term Health Impacts of Prenatal Exposure to PFOA in Mice
- State Update: New Jersey Drinking Water Guidance for PFOA
- State Update: Development of NCPHG for Total PFOA and PFOS
- State Update: Perfluorinated Chemicals in Minnesota—Derivation of Health Protective Criteria
- Cardiac, Diabetic and Cancer-related Risks from Chronic Arsenic Exposure in Inner Mongolia
- Arsenic Susceptibility and In Utero Effects
- Arsenic Mode of Action and Developing a Biologically Based Dose Response Model
- Overview: NHEERL's Endocrine Disruptors Research Program
- Emerging Issues in Endocrine Disrupting Chemical Research: From CAFO to Cumulative Risk
- Brominated Flame Retardants: Why Do We Care?
- Emerging Contaminants: Water Quality Criteria Derivation Issues
- Developmental Origins of Health and Disease: Implications for Toxicology
- Research on Defined and Complex Mixtures of Disinfection ByProducts
- Recreational Water Research: The NEEAR Study
- NTP Studies of Hexavalent Chromium
- State Approaches for Risk Assessment of Chrome 6
- Health Risk Assessment of Engineered-Manufactured Nanomaterials: Research Challenges and Preliminary Findings
- Nanotechnology and Regulatory Issues

This report summarizes the presentations and discussions. Appendix A is the agenda, and Appendix B is a list of attendees. Copies of most speakers' handouts are provided. Where handouts are not provided, please contact the speaker by phone or e-mail for more information.

Day Two: Thursday, October 18, 2007
Hilton Durham near Duke University
Durham, North Carolina

Bill Russo
U.S. Environmental Protection Agency
Overview of EPA' s Office of Research and Development (ORD) and National Health and Environmental Effects Research Laboratory

Bruce Mintz
U.S. Environmental Protection Agency
EPA Research & Development
National Exposure Research Laboratory
Water-related Research Overview

Abdel Kadry
U.S. Environmental Protection Agency
U.S. EPA's Integrated Risk Assessment System (IRIS): An Update on the Program

Scott Masten
Environmental Toxicology Program, NIEHS
Current Research and Testing Activities in the National Toxicology Program

Ambika Bathija
U.S. Environmental Protection Agency
OST/HECD/OW Update

Clement Welsh
Agency for Toxic Substances and Disease Registry
Overview of ATSDR Activities for PFOA

Christopher Lau
U.S. Environmental Protection Agency
Perfluorinated Chemicals: Overview of EPA's Research Activities

Suzanne Fenton
U.S. Environmental Protection Agency
Immediate & Long-term Health Impacts of Prenatal Exposure to PFOA in Mice

Gloria Post
New Jersey Department of Environmental Protection
New Jersey Drinking Water Guidance for PFOA

Luanne Williams
North Carolina Department of Health and Human Services
Calculation of a North Carolina Public Health Goal (Health-based Drinking Water Level) for Total Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) Level

Helen Goeden
Minnesota Department of Health
Perfluorinated Chemicals in Minnesota– Derivation of Health Protective Criteria

Judy Mumford
U.S. Environmental Protection Agency
Cardiac, Diabetic and Cancer-related Risks from Chronic Arsenic Exposure in Inner Mongolia

David Thomas
U.S. Environmental Protection Agency
Arsenic-Susceptibility and In Utero Effects

Doug Wolf
U.S. Environmental Protection Agency
Arsenic Mode of Action and Developing a Biologically Based Dose Response Model

Overview of EPA' s Office of Research and Development (ORD) and National Health and Environmental Effects Research Laboratory

Bill Russo
U.S. Environmental Protection Agency
(919) 541-7869
russo.bill@epa.gov

Visuals follow. Please contact the speaker for more information.

EPA United States Environmental Protection Agency

Overview of EPA' s Office of Research and Development (ORD)

Presented to FEDERAL-STATE TOXICOLOGY AND RISK ANALYSIS COMMITTEE (FSTRAC), October 18, 2007

William E. Russo, NHEERL Asst. Laboratory Director for Water and Land

EPA United States Environmental Protection

Environmental Protection Agency

EPA Mission:
Protect human health and safeguard the natural environment – air, water, land – upon which life depends

Regulatory Agenda

Scientific Foundation

Implementation, Execution

PROGRAM OFFICES
(e.g., Air, Water, Pesticides/Toxics)
Policies, Regulations ■ Congressional Deadlines

OFFICE OF RESEARCH AND DEVELOPMENT

REGIONS
Primary Interface with States

NERL
Exposure

NHEERL
Effects

NCEA
Risk Characterization

NRMRL
Risk Management

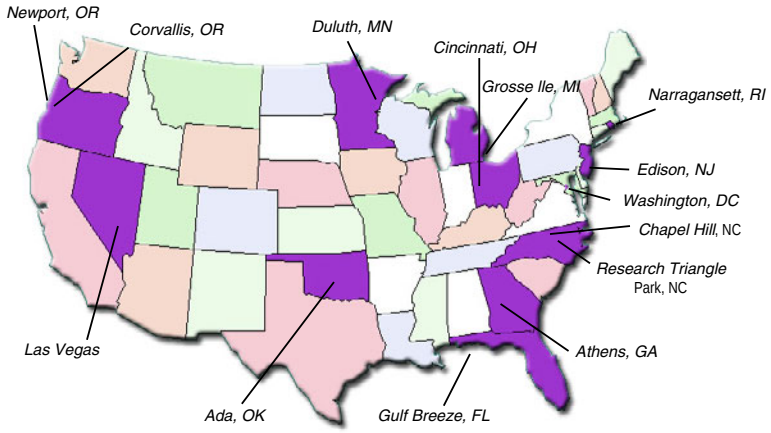
NCER
Extramural research

NHSRC
Homeland security research

NCCT
Computational tools

ORD Locations

- 3 National Laboratories
- 4 National Centers
- 2 Offices
- 13 Locations



EPA's Mission

Protect human health and safeguard the natural environment upon which life depends.

ORD provides the scientific foundation to support EPA's mission.

- **Conducts research and development** to identify, understand, and solve current and future environmental problems
- **Provides responsive technical support** to EPA's Programs and Regions
- **Collaborates with scientific partners** in academia other Federal Agencies, states and tribal governments, private sector organizations, and foreign nations
- **Exercising leadership** in addressing emerging environmental issues and advancing the science and technology of risk assessment and risk management

Multi-year Research Planning

- Clean Air
- Contaminated Sites and Hazardous Waste
- Drinking Water
- Endocrine Disruptors
- Global Change
- Homeland Security
- Mercury
- Safe Pesticides/Safe Products
- Water Quality

- Ecological Research
- Economics & Decision Sciences
- Human Health
- Pollution Prevention

Emerging Areas

- Energy
- Nanotech
- Sustainable Technologies
- Accountability
- Computational Toxicology

National Health and Environmental Effects Research Laboratory

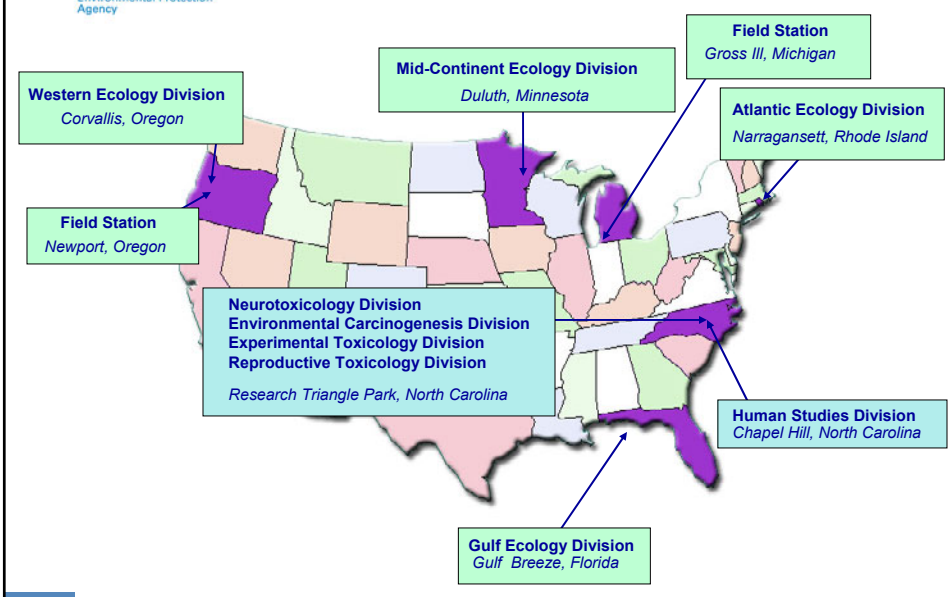
NHEERL's mission is to determine the impacts of environmental stressors on human and ecosystem health and the degree to which those stressors cause harm …

Multi-prong Approach to Research Emphasizing Lab-Field Interface

- **Toxicology** ranging from molecular biology/mechanisms to functional outcomes
- Environmental **monitoring** including EMAP
- Epidemiological and ecological **field studies** including environmental, exposure and effects assessment
- Predictive **modeling** including PBTK/BBDR, population effects, and large ecosystem models
- **Clinical studies** including controlled human exposure studies and in vitro systems

- Includes Core and Problem Driven Research

NHEERL Locations



Examples of Problem Driven Water Related Research

Water

- Develop a biologically based dose-response model for inorganic arsenic.
- Development of testing methods for identification of potential ecological impacts from CAFOs
- Model the relationship between habitat alteration and ecological response in streams and coastal systems.

Communities & Ecosystems

- Develop test methods for prioritization and screening
- Validate large scale fish and avian population models to predict ecosystem level effects from exposure or habitat damage.

Core Human Health Research Areas for NHEERL

- Predicting aggregate and cumulative risk (e.g., multistressors)
- Assessing effects on susceptible populations
- Applying molecular/computational methods in a systems toxicology approach to risk assessment
- Assessing the public health impact of environmental decisions and actions

NHEERL Research Presented

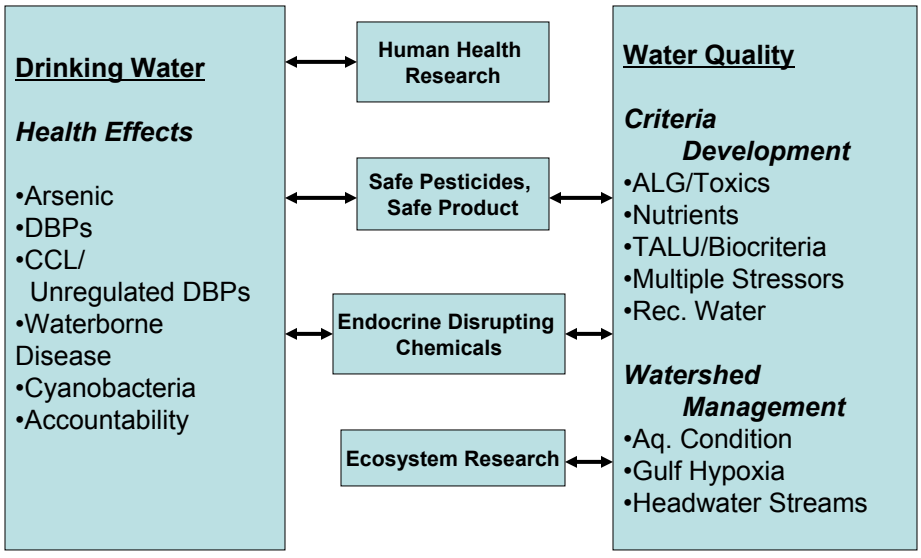
- Clean Air
- Contaminated Sites and Hazardous Waste
- ***Drinking Water***
- ***Endocrine Disruptors***
- Global Change
- Homeland Security
- Mercury
- ***Safe Pesticides/Safe Products***
- ***Water Quality***

- ***Ecological Research***
- Economics & Decision Sciences
- ***Human Health***
- Pollution Prevention

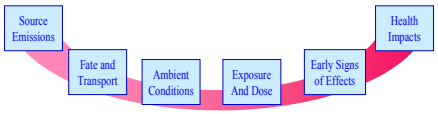
Emerging Areas

- Energy
- ***Nanotech***
- Sustainable Technologies
- ***Accountability***
- ***Computational Toxicology***

Water Related Research at NHEERL



Future Research Directions in Tox Testing

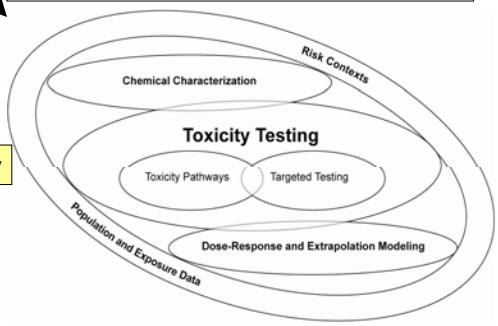


Source to Effects Risk Paradigm

Research programs to transition from **source to effects** research, our current paradigm to that proposed in the recent NRC report.

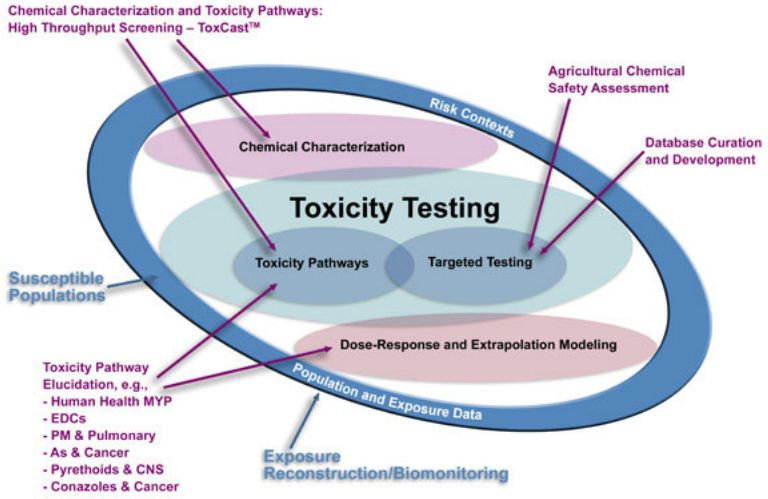
- Supports emerging needs for screening and prioritization of chemicals/complex mixtures / investigations of relative toxicity
- Provides context for biomarkers research in terms of identifying markers of activation of key toxicity pathways, disease, and susceptibility.
- Efforts underway in both the health and ecological effects program

NRC: Tox Testing in 21st Century



NAS Vision of Toxicity Testing and Assessment in the 21st Century

EPA United States Environmental Protection Agency



National Academy of Sciences , 2007

Summary

- NHEERL's water research program is focused on science questions associated characterizing health and ecological effects of contaminated waters
  - Drinking Water Health Effects Research
    - Arsenic; DBPs, CCL/Unregulated DBPs, Waterborne Disease, Cyanobacteria, linking actions to reduced health outcomes
  - Water Quality Criteria Development
    - ALG/Toxics, Nutrients, TALU/Biocriteria, Multiple Stressors, Rec. Waters
  - Watershed Management
    - Technical support for assessing Aquatic Condition, Gulf Hypoxia, Headwater Streams, watershed management tools

Summary

- Water research needs are also cross cutting and addressed through research efforts in multiple Multi-Year Plans
  - **Human Health Research (**Arsenic Mode-of Action, Biologically Based Dose Response Model, Susceptibility, Accountability)
  - **Safe Pesticides, Safe Products** (Screening and Prioritization, Probabilistic Eco Risk Assessment, PFOS/PFOA)
  - **EDCs** (Improved understanding, Determining impacts, support for EPA's EDC screening and testing program)
  - **Ecological Research** (EMAP, Ecosystem Services)

Questions, Answers, and Comments

Q. Bob Howd: What's a CAFO?

A. Bill Russo: Concentrated animal feeding operation.

Q. Ed Ohanian: Thank you. That was a very good synopsis of activities, but do you have a Web site for the membership in case they want to get into more detail regarding the research?

C. Bill Russo: For the multiyear plans?

Q. Ed Ohanian: Yes. That would be great in case they want to go to it and they have some additional questions. And maybe you can also provide contact names.

C. Bill Russo: The Web site is http://www.epa.gov/osp/myp.htm. The contacts (also available via the Web link) are listed below.

Goal 1: Air
Air Toxics - Dan Costa
Particulate Matter - Dan Costa

Goal 2: Water
Drinking Water - Audrey Levine
Water Quality - Chuck Noss

Goal 3: Land
Land - Randy Wentsel

Goal 4: Communities and Ecosystems
Ecological Research - Rick Linthurst
Human Health - Hugh Tilson
Human Health Risk Assessment - John Vandenberg
Global Change - Joel Scheraga
Mercury - Joel Scheraga
Endocrine Disruptors - Elaine Francis
Safe Pesticides/Safe Products - Elaine Francis

Goal 5: Compliance and Environmental Stewardship
Economics and Decision Science - William Wheeler
Science and Technology for Sustainability - Gordon Evans

As the multiyear plans are updated, they will be placed on the Web site.

C. Ed Ohanian: Thank you.

EPA Research & Development National Exposure Research Laboratory Water-related Research Overview

Bruce Mintz
U.S. Environmental Protection Agency
(919) 541-0272
mintz.bruce@epamail.epa.gov

Visuals follow. Please contact the speaker for more information.

NERL is comprised of several divisions with diversified research specialties. NERL conducts research and development that leads to improved methods, measurements and models to assess and predict exposures of humans and ecosystems to harmful pollutants and other conditions in air, water, soil, and food.

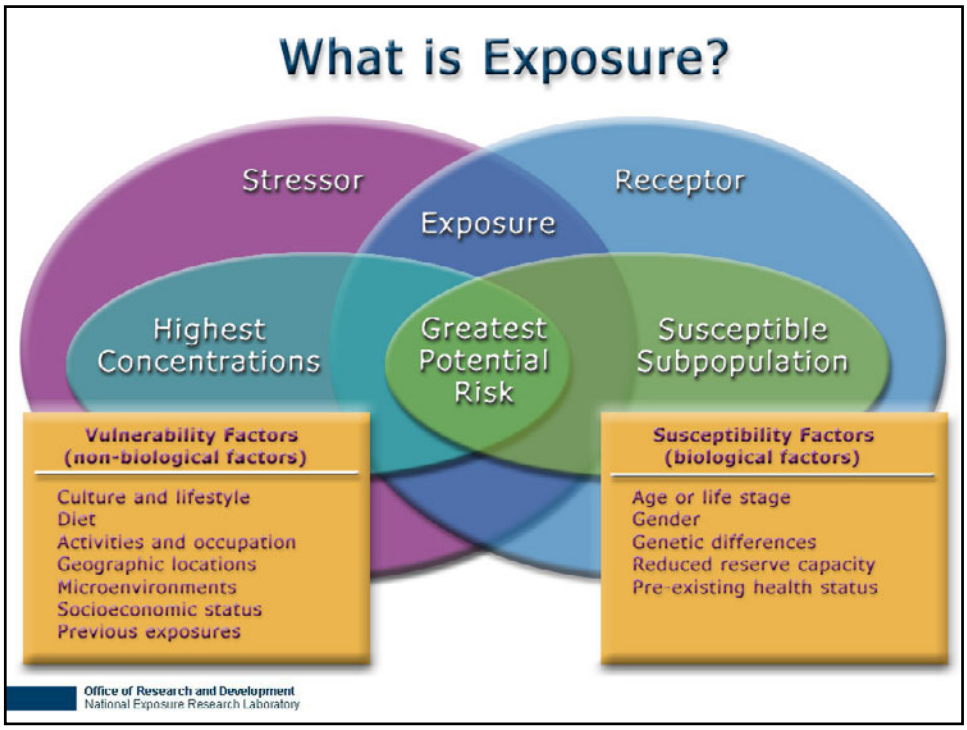
NERL's Water Quality Research Program is directed to help ORD achieve three long term goals: (1) improved water quality criteria and monitoring for identifying impaired waterbodies (2) improved diagnostics, including forecasting techniques, to identify causes and sources of impairment; and (3) improved selection, placement and management of sustainable watershed protection and restoration technologies, including techniques for forecasting the ecologic, economic, and human health benefits of management alternatives.

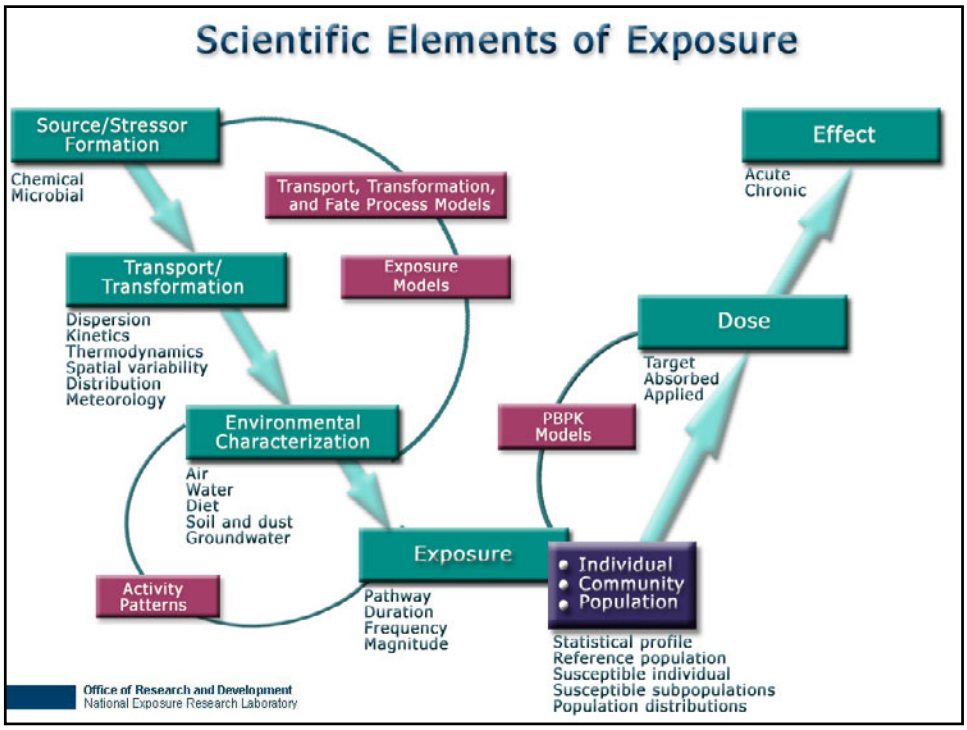
NERL's Drinking Water Research Program is directed to help ORD achieve three long term goals: (1) provide scientific support for EPA's implementation and reevaluation of existing regulations; (2) provide a scientific foundation for decisions on emerging and currently unregulated contaminants; and (3) provide data, tools and technologies to protect source waters and distribution systems.

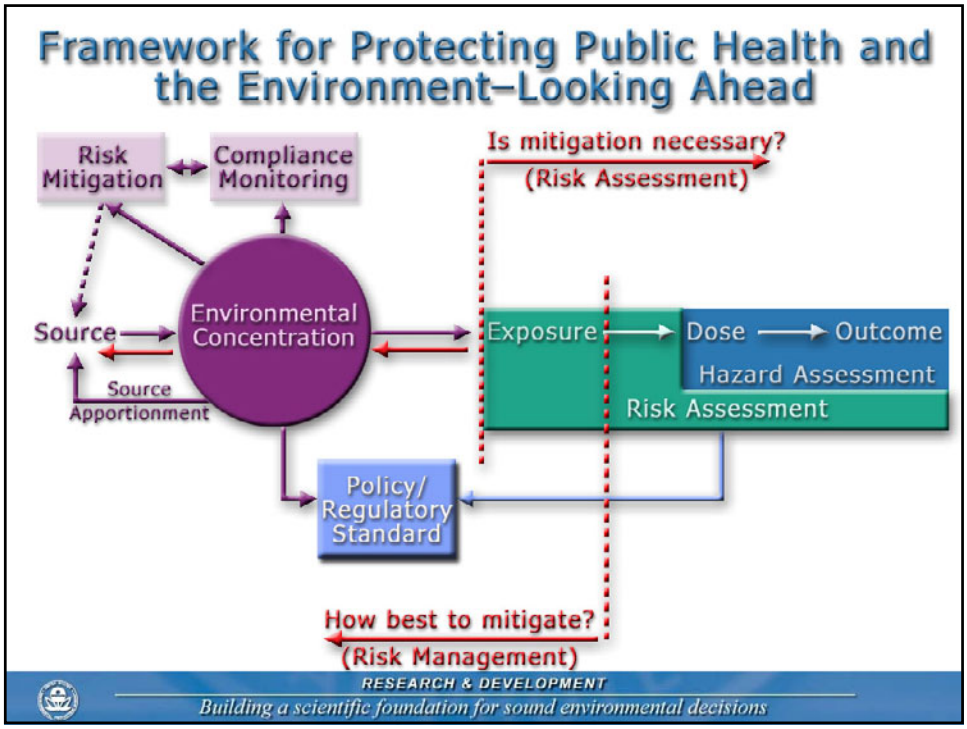
EPA Research & Development

National Exposure Research Laboratory
Water-related Research Overview

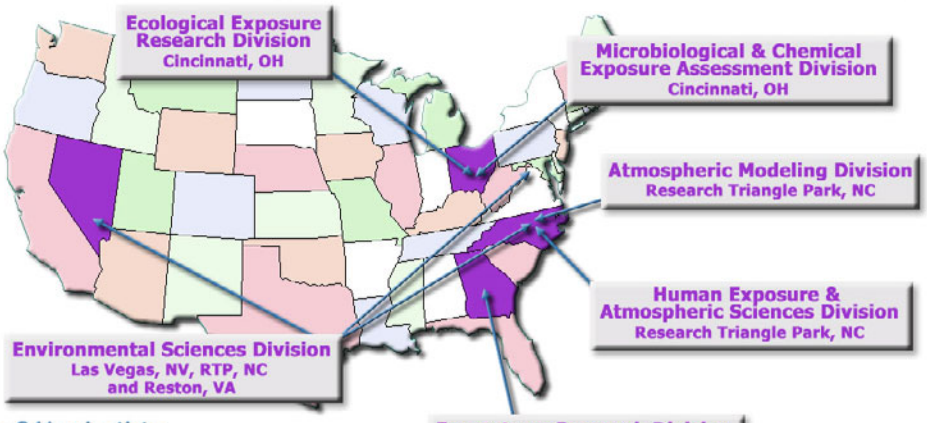
Briefing for FSTRAC
October 18, 2007
Durham, NC




Scientific Elements of Exposure
Source/Stressor Formation
Chemical
Microbial
Transport, Transformation, and Fate Process Models
Effect
Acute
Chronic
Transport/ Transformation
Exposure Models
Dispersion
Kinetics
Thermodynamics
Spatial variability
Distribution
Meteorology
Dose
Target
Absorbed
Applied
Environmental Characterization
PBPK Models
Air
Water
Diet
Soil and dust
Groundwater
Exposure
Individual
Community
Population
Activity Patterns
Pathway
Duration
Frequency
Magnitude
Statistical profile
Reference population
Susceptible individual
Susceptible subpopulations
Population distributions
Office of Research and Development
National Exposure Research Laboratory


Framework for Protecting Public Health and the Environment–Looking Ahead
Risk Mitigation
Compliance Monitoring
Is mitigation necessary?
(Risk Assessment)
Environmental Concentration
Source
Source Apportionment
Exposure
Dose
Outcome
Hazard Assessment
Risk Assessment
Policy/ Regulatory Standard
How best to mitigate?
(Risk Management)
RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

National Exposure Research Laboratory



- 341 scientists
- 73 managers and administrative staff
- 26 post docs
- $107 million budget including an extramural budget of $37.4 million
- 112 peer-reviewed articles (2005)

Drinking Water Research

- Implementation and reevaluation of existing regulations
  - Arsenic Rule Research
  - Ground Water / Surface Water Treatment Rule Research
- Decisions on emerging and currently unregulated contaminants (CCL, DS)

Context for DW Research

- Does the contaminant occur at levels posing potential health risks (SDWA)?
- Will new regulations provide a meaningful risk reduction opportunity (SDWA)?
- How effective are implemented rules (OMB/PART)?

Arsenic Rule Research

- Distribution system and treatment residual solids
- Arsenic in food
- Mode of action determinations

Distribution system and treatment residual solids

Problem: uncertainty regarding potential health risks from the mobility of arsenic from distribution system solids and from treatment residuals

Research: apply extraction techniques to evaluate how various drinking water chemistries and treatment changes may influence the release of arsenic.

Arsenic in Food

Problem: uncertainty how much arsenic in US diet contributes to total arsenic exposure/risk

Research:

- estimating bioaccessibility of arsenic species from different target foods
- preliminary database of arsenic species in target foods

Mode of Action Determinations

Problem: uncertainty regarding reactive intermediates in the inorganic arsenic detoxification process

Research: developing analytical techniques for developing biomarkers and dosimetric data for epi, pharmacokinetic and mode of action studies

Ground Water / Surface Water Treatment Rule Research

Problem: the majority of *Cryptosporidium* and *Giardia* are not recovered in current measurement methods, and the viability and speciation are difficult to determine

Research: developing improved processing and detection techniques

Ground Water / Surface Water Treatment Rule Research

Problem: estimates of human exposures to viruses from ground waters and the effectiveness of existing or proposed revised regulations are highly uncertain

Research:

- evaluating the performance of improved viral detection and measurement methods
- developing a non-invasive saliva-based method for measuring individual human exposure

CCL Research

Problem: analytical methods are needed for UCMRs and compliance monitoring

Research: developing methods for

- organotins
- perfluorinated alkyl compounds (PFCs)
- solvent stabilizers and water soluble volatile organics such as 1,4-dioxane
- previously unidentified DBPs
- pathogens, including several bacteria and toxins (*Aeromonas*, *Helicobacter*, *Mycobacterium*, cyanobacterial toxins), protozoa (microsporidia, *Toxoplasma*, and *Cyclospora*) and enteric viruses

CCL Research – cont.

Problem: innovative methods are needed to detect, classify and prioritize contaminants

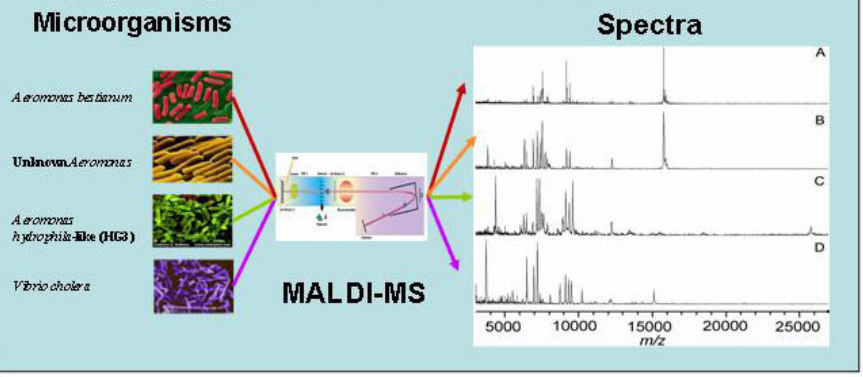
Research:

- molecular methods (e.g., qPCR, microarrays)
- proteomics to characterize pathogen speciation and viability/infectivity
- evaluating the utility of Virulence Factor Activity Relationships (VFARs)

Proteomics for Better Pathogen Characterization

Sample Analysis

MALDI-MS was used to create a mass spectral fingerprint (3000 *m/z* -30,000 *m/z*) for each strain/isolate studied. The mass values observed were used to differentiate between the species of *Aeromonas* as well as other related genera (*Vibrio* and *Plesiomonas*). This comparison is possible because different species of bacteria express different proteins. Below is an example of the spectra observed for different microorganisms.



CCL Research – cont.

Problem: uncertainty and public concern about potential adverse human health effects from PPCPs

Research:

- identifying which PPCPs
  - are found downstream from wastewater treatment plants
  - enter drinking water treatment facilities
- evaluating the effectiveness of various removal technologies
- identifying possible transformation by-products

Water Quality Research

- Criteria development
  - Recreational water
  - Biossessment/biocriteria
  - Emerging contaminants
  - Headwaters/wetlands
- Assessing conditions and diagnosing sources/causes
  - Landscape assessment
  - Forecasting effectiveness of management options (e.g., TMDL modeling)

Recreational Water Criteria Research

Problem: Beach Act requires rapid indicators and revised criteria

Research:

- Development/evaluation of rapid indicators
- Fate/transport of indicators/pathogens
- Predictive modeling

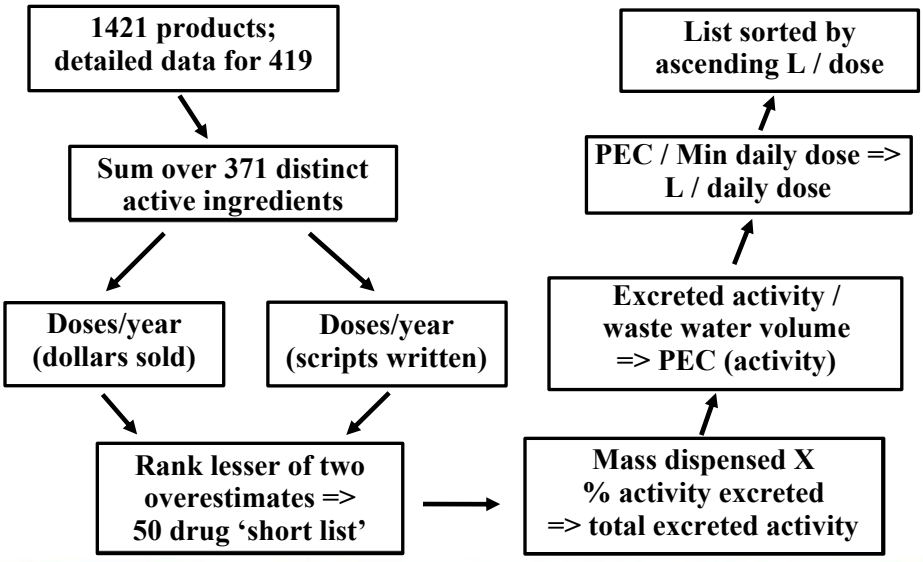
Emerging Contaminants Research

Problem: uncertainty about potential adverse ecological and human health effects

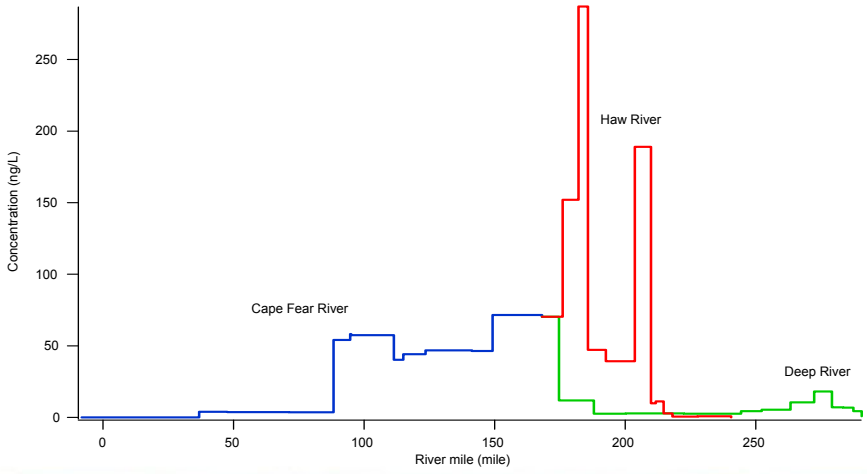
Research:

- Bioinformatic approach to PPCP priority-setting
- Genomic and chemical indicators of exposures and effects from EDCs and PPCPs on aquatic life from sewage discharges and CAFOs
- Methods and exploratory occurrence data for PPCPs and PFOAs in surface waters, sewage and biosolids
- Genetic methods for rapid detection of ballast organisms

PPCPs Prioritization Using Bioinfomatics



PFOS in river water (ng/L) on the Cape Fear River Basin, NC



Bioassessment/Biocriteria Research

Problem: chemical and physical criteria are incomplete measures of water quality conditions

Research: development of bioassessment methods:

- for poorly monitored water bodies (e.g., large rivers)
- based on DNA identification and evaluation of genetic diversity within species

Headwaters and Wetlands Research

Problem: value of headwaters and wetlands needs to be documented

Research: developing tools to assess the hydraulic connectivity aka.“significant nexus”

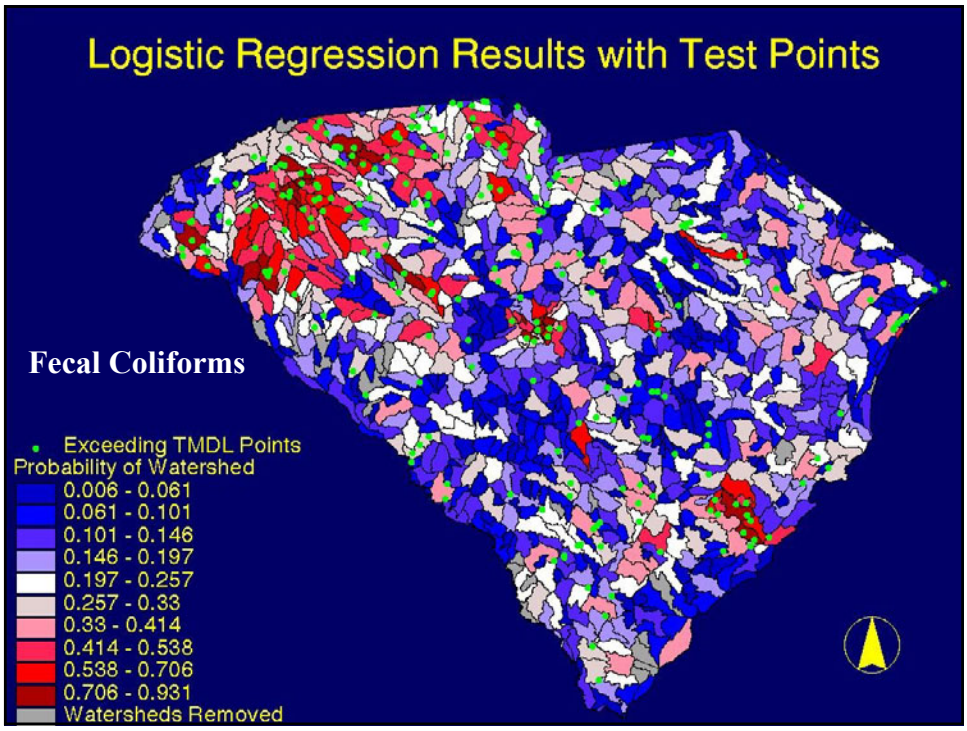
Landscape Assessment Research

Problem: States cannot

- monitor all of their water bodies
- restore all of their impaired waters

Research: demonstrating use of landscape assessments for

- targeting monitoring
- prioritizing restoration



Forecasting Effectiveness of Management Options

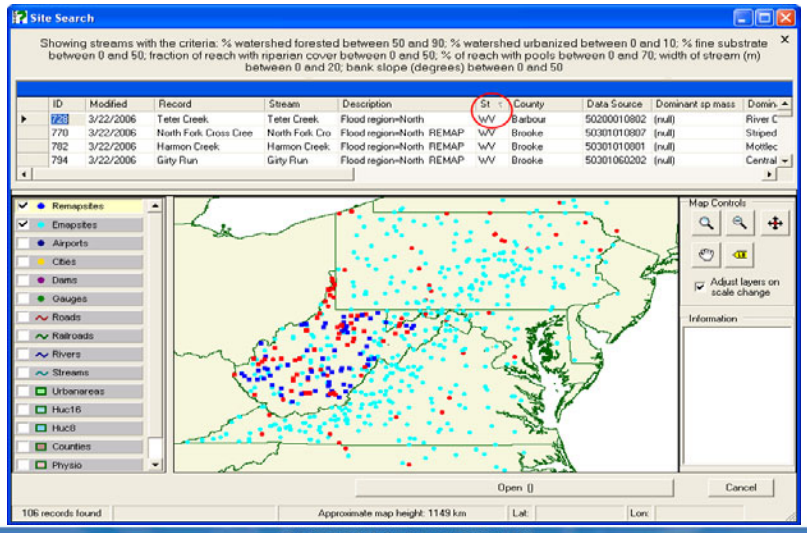
Problem:

- States/Regions are required to calculate and allocate TMDLs
- Watershed management resources need to be invested effectively

Research/Tech Support:

- Nutrient, sediment and Hg fate/transport models
- Watershed and Water Quality Modeling Technical Support Center for model distribution, training and technical outreach

"What-If" Model: Display of Query Results



Future Strategic Research Directions

Drinking Water

- use of biofilms to estimate human exposures from microbes in distribution systems
- data/models for improved exposure assessments
- biomarkers of human exposure to microbes from drinking water
- advanced detection methods

Future Strategic Research Directions

Water Quality

- Applied integrated modeling and monitoring for prioritization, diagnostics and forecasting
- Research to improve micro risk analyses (collaboration with OW, NCEA, NHEERL)
  - Characterization of emerging pathogens
  - Fate and transport
  - Impact of factors such as secondary spread
- Research to support risk analyses of emerging contaminants (e.g., PPCPs, nanoparticles, NISs)

Questions, Answers, and Comments

Q. Gloria Post: Can you talk about the research you were doing on arsenic in food? How could that be applied in the drinking water risk assessment? How could that information be used since we are already regulating arsenic at 4 orders of magnitude above what the target based on risk alone would be?

A. Bruce Mintz: It could be used in two ways. One is in the risk quantification area. Because of the costs involved in managing arsenic, there is still a lot of concern that we don't know everything about low-dose arsenic exposure. A lot of the current quantification is based on total arsenic in looking at the Taiwanese data. There is a lot of uncertainty about how much of that exposure was from food. Frankly, the current assumption is that a lot of it is from drinking water and if more of it was from food than we considered in the dose-response quantification, that would affect the dose-response. The second area where the food data are very important is in the health risk reduction benefit assessment—if and when EPA's Office of Water ever revises an arsenic rule through the 6-year review process. It's very difficult to estimate what current U.S. population risks are from arsenic and how they would change based on some rulemaking. So, the more information we have about the different toxic species of arsenic in food, the more we can better estimate current or projected U.S. population risks.

C. Gloria Post: Thanks.

Q. Perry Cohn: Thanks, Bruce. I have a couple of questions. One is just a more specific answer on the saliva-based methods that you had mentioned. Are you looking for antibodies or organisms?

A. Bruce Mintz: We're talking about antibodies in saliva.

Q. Perry Cohn: In terms of the CCL research, there are a number of methodological studies going on with analytical methods. I'm just curious with regard to a few of them that I'm interested in, such as the perfluorinated compounds as well as the pathogens. What kind of timeline do you see for getting those out?

A. Bruce Mintz: It depends on the media and the use of the method. From what I understand, there are lots of people working on PFOA methods. Some are more research-oriented, whereas I believe our Cincinnati lab has developed some that are more applicable for drinking water utilities to apply. If that's what you're interested in, I could get you more information on the timeline for that.

Q. Perry Cohn: Yes, for things like quantitative polymerase chain reaction (qPCR) and so on. It would be interesting to see a little more detail about how those things are progressing, at least in terms of tools that we have for waterborne disease surveillance.

C. Bruce Mintz: The pathogens are much more difficult than the chemicals. With the pathogens, we've been somewhat successful in developing detection methods. We're trying to put emphasis on the sample processing. We have a pretty major effort now for the viruses and protozoa and the processing of the water sample to get better recovery and preservation of the viruses and protozoa. That has been one of the issues in the past. We say, "Yeah, we've developed a method to detect and measure an organism," but it's really not ready to put out for people to use.

C. Luanne Williams: I just wanted to let the folks here, as well as EPA, know that we are finding in North Carolina microcystin (blue-green algae) toxins in public finished water supplies out in the distribution. Currently, we are undergoing a study to see if there are seasonal trends. But we are finding levels that are at the World Health Organization's guideline value—I think it is 1 μg/L for drinking water. We have a database in North Carolina called NC DETECT (North Carolina Disease Event Tracking and Epidemiologic Collection Tool), which allows us to look at respiratory-related and gastrointestinal-related emergency room hospital visits, and we are seeing a connection between an increased number of gastrointestinal-related and respiratory-related visits and elevated microcystin toxins. We hope to publish that and get that out. I'd encourage EPA to put that on your radar and to consider in the future requiring these public water supplies to responsibly monitor for these toxins and to possibly evaluate respiratory endpoints for these blue-green algae toxins.

Q. Scott Stoner: I'm not that familiar with the bioinformatics. Could you talk a little more about what that is and how it is used to narrow down these large lists of emerging contaminants?

A. Bruce Mintz: I could probably get you more information on it. Offhand my recollection is that it's looking at the available data on production and other indicators of potential exposure. And then on the effects side, I'm not sure exactly what indicators of effects are being used. But it's basically combining indicators of exposure and effects and basically trying to rank the thousands of contaminants. It's done in a worst-case sort of way so that if it doesn't indicate a potential risk, there's some comfort that you don't need to do further research—that the ones that ranked higher were probably the ones to look at.

Q. Scott Stoner: It's more of a CCL process?

A. Bruce Mintz: In some ways it is. But it is also trying to get at ecological risk, which is quite different.

Q. Helen Goeden: Is the focus mostly on therapeutic types of agents, then, in that screening process?

A. Bruce Mintz: I don't think so. I don't think it is limited to that. I'll see if I have anything to distribute to folks on that.

C. Ambika Bathija: I think we need to move on. I want to thank Bruce Mintz and Bill Russo for the excellent overview of the activities in their labs. Also, I want to thank Bruce for helping us put together that ISEA-coordinated meeting yesterday. It was a very good meeting. I also want to thank Bill Russo for helping us put together the agenda for today and tomorrow.

U.S. EPA's Integrated Risk Information System (IRIS): An Update on the Program

Abdel Kadry
Integrated Risk Information System, U.S. Environmental Protection Agency
(202) 564-1645
kadry.abdel@epa.gov

Visuals follow. Please contact the speaker for more information.

The Integrated Risk Information System (IRIS) program publishes the U.S. Environmental Protection Agency's (EPA) scientific positions on potential adverse health effects that may result from exposure to potential environmental hazards. This publicly available database houses health assessments that serve as key resources in informing risk-based decision-making. IRIS is a repository not only of toxicity information for EPA Program Offices and Regional Offices, but an important source of hazard identification and dose-response information for other federal and state agencies, as well as national, international, public and private organizations. The heavy reliance on IRIS is exemplified by the over 700,000 'web hits' per month from over 100 countries. The current process for the development of an IRIS assessment includes several layers of review within and outside of the EPA, before it is posted on the IRIS database. This process allows for other agencies and interested parties to review and comment on the draft assessment before it is finalized. The U.S. EPA is incorporating advances in the field of risk assessment in its assessment development process. These include greater use of mode-of-action data to inform hazard identification and cancer characterization and to identify appropriate low-dose extrapolation methods in cancer assessments, quantitative methods for expressing uncertainty, physiologically-based pharmacokinetic modeling, and approaches for assessing mixtures. The recent milestones are illustrated and discussed.

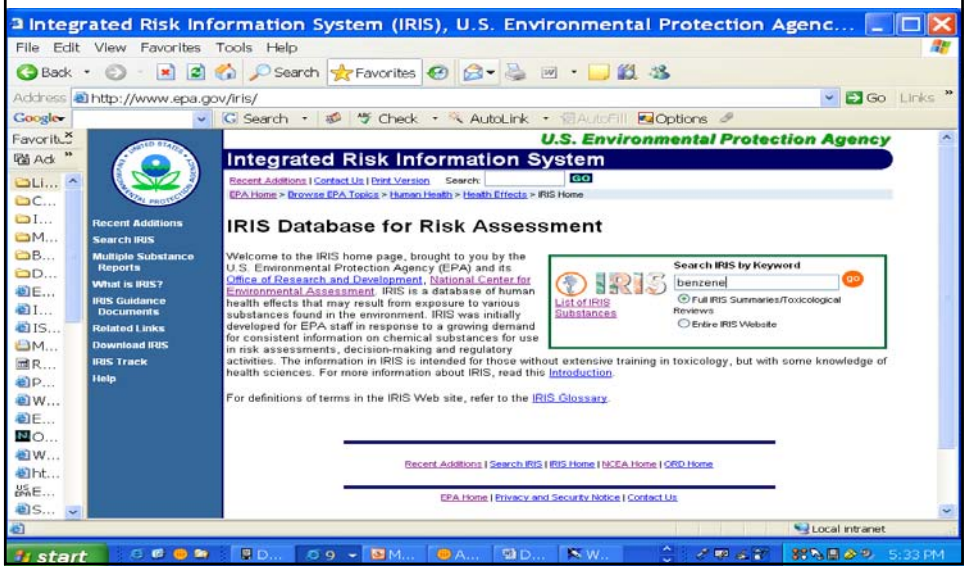
U.S. EPA's Integrated Risk Information System (IRIS): An Update on the Program

Abdel Kadry,,DVM, PhD., DABT, Program Director
Integrated Risk Information System
National Center for Environmental Assessment
Research and Development, USEPA, Washington, DC

Integrated Risk Information System (IRIS)

- Provides EPA scientific positions on potential adverse health effects that may result from exposure to chemical substances found in the environment
- Oral reference doses and inhalation reference concentrations for non-cancer endpoints
- A weight of evidence description (e.g., known human carcinogen), oral slope factors, and inhalation unit risks for cancer
- EPA risk assessors combine IRIS toxicity values with scenario-specific exposure values to estimate risk
- Source of toxicity information to inform risk-based decision-making; founded on EPA guidelines for health risk assessment
- Fosters consistent risk assessments across EPA Programs and Regions
- Supports NAS risk assessment paradigm

IRIS Database Home Page
www.epa.gov/iris



IRIS Users

- IRIS database: www.epa.gov/iris
- Coverage: ~540 chemicals
- Users
  - EPA Program Offices and Regional Offices
  - Other Federal agencies
  - State and local agencies
  - International agencies
  - Public - including academia, regulated industries, environmental organizations, individuals

2006 IRIS Web Site Hits

Web Action	January	August	December
Successful requests	688,511	668,520	701,181
Average successful requests per day	22,213	21,565	22,619
International hits	112 Countries	113 Countries	117 Countries

IRIS Management and Scientific Staff

Program director: Abdel Razak Kadry, DMV, PhD, DABT

Toxic Effects Characterization Team

Jamie Strong, PhD, Team Leader (Acting)
Martin Gehlhaus, MPh
Channa Keshava, PhD
Kathleen Newhouse, MS
Andrew Rooney, PhD
Reeder Sams, PhD
Gillian Backus, PhD
Geoffrey Patton, PhD

Management Support
Christine Ross, Brenda Washington, Laurice Stewart , Agnes Robinson

Toxicology, Epidemiology & Statistics Team

Karen Hammerstrom, J.D., Team Leader
Ted Berner, MS
Glinda Cooper, PhD
Karen Hogan, MS
Samantha Jones, PhD
Allan Marcus, PhD
Amanda Persad, PhD, DABT
Susan Rieth, MPh
John Whalan
Diana Wong, PhD, DABT
Jenney Li, PhD
Audrey Galizia, PhD
Ghazi Dannan, PhD (detail)

EPA United States Environmental Protection Agency

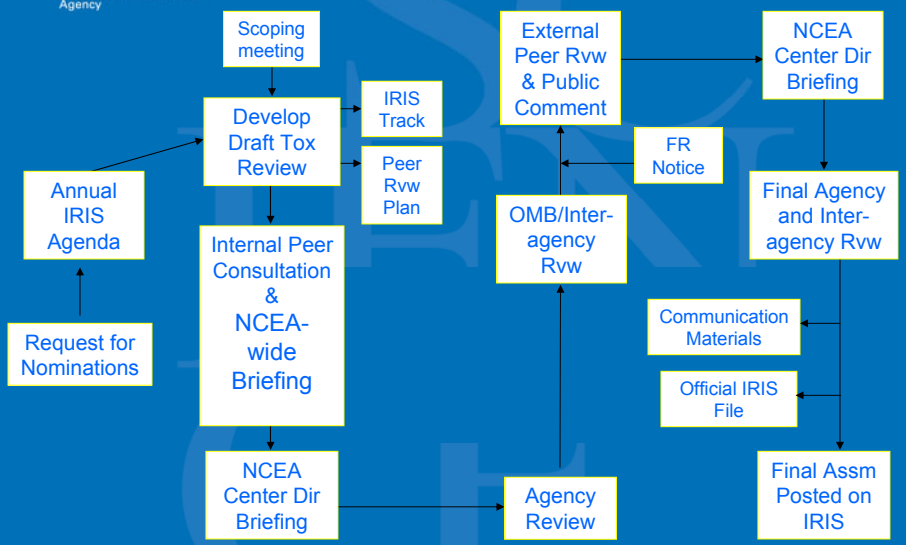
Current Process for Assessment Development and Review

- Annual FR Notice of IRIS agenda; data call
- Literature search and review
- EPA develops draft assessment
- Internal peer review, IRIS Agency Review
- Interagency review
- External peer review with public comment period
- Final EPA approval and posting on IRIS database

This process is documented in IRIS Standard Operating Procedures, which are updated annually

EPA United States Environmental Protection Agency

2007 IRIS Process Chart



The IRIS Annual Agenda

- Nominations solicited annually from EPA Program and Regional Offices
- 101 chemicals and chemical classes nominated in 2004/2005
- 25 chemicals and chemical classes nominated in 2007/2008

Criteria for selection

- Potential public health impact;
- EPA statutory, regulatory, or program-specific implementation needs;
- Availability of new scientific information or methodology that might significantly change the current IRIS information;
- Interest to other governmental agencies or the public; and
- Availability of other scientific assessment documents that could serve as a basis for an IRIS assessment.

2005/2006 New Starts

New starts in 2005:

- Butyl benzyl phthalate (OSWER, Region 2 & 10)
- Cerium (OTAQ, Region 4)
- Platinum (OTAQ, Region 4)
- 2-hexanone (OSWER)
- Naphthalene (non-cancer) (The Agency reviewers)
- 1,1,2,2-tetrachloroethane (OAQPS, Regions 1 & 4)
- Hexachloroethane (OSWER, Region 1)

New start in 2006

- Asbestos (cancer) (OSWER, Regions 2, 4, 10)

Assessments in Progress

- acetaldehyde
- acrylamide
- acrylonitrile
- arsenic
- asbestos
- benzo(a)pyrene
- beryllium (cancer effects)
- bromobenzene
- butyl benzyl phthalate
- cadmium
- carbon tetrachloride
- cerium
- chloroethane
- chloroform
- chloroprene
- cobalt
- copper
- dibutyl phthalate
- 1,2-dichlorobenzene
- 1,3-dichlorobenzene
- 1,4-dichlorobenzene
- 1,2-dichloroethylene
- di(2-ethylhexyl)adipate (DEHA)
- di(2-ethylhexyl)phthalate
- 1,4-dioxane
- ethanol
- ethyl tertiary butyl ether
- ethylbenzene
- ethylene dichloride
- ethylene glycol monobutyl ether (cancer effects)
- ethylene oxide (cancer effects)
- formaldehyde
- hexachlorobutadiene
- hexachloroethane

10

Assessments in Progress

- RDX (hexahydro-1,3,5-dintirotriazine)
- 2-hexanone
- hydrogen cyanide
- isopropanol
- kepone
- methanol
- methyl tert-butyl ether (MTBE)
- methylene chloride (dichloromethane)
- mirex
- naphthalene (inhalation route)
- nickel (soluble salts)
- nitrobenzene
- PAH mixtures
- pentachlorophenol
- perfluorooctanoic acid - ammonium salt (PFOA)
- perfluorooctane sulfonate - potassium salt (PFOS)
- phosgene (acute exposure)
- platinum
- polybrominated diphenyl ethers
- polychlorinated biphenyls (PCBs) (noncancer endpoints)
- propionaldehyde
- refractory ceramic fibers
- styrene
- 2,3,7,8-TCDD (dioxin)
- 1,1,2,2-tetrachloroethane
- tetrachloroethylene
- tetrahydrofuran
- thallium
- trichloroacetic acid
- trichloroethylene
- 1,2,3-trichloropropane
- uranium compounds
- vinyl acetate

11

Major Assessments Underway

- Acrylamide
- Acrylonitrile
- Arsenic
- Asbestos
- Ethylbenzene
- Ethanol
- Ethylene Oxide
- Formaldehyde
- MTBE
- Naphthalene
- Perchloroethylene
- Trichloroethylene

2007 New Starts

- alkylates
- ammonia
- antimony
- tert-amyl methyl ether (TAME)
- bisphenol A (BPA)
- biphenyl
- n-butanol (butyl alcohol)
- tert-butyl alcohol (TBA)
- carbonyl sulfide
- chromium (VI), hexavalent chromium
- diethyl phthalate (DEP)
- diisopropyl ether (DIPE)
- 4,4-dimethyl-3-oxahexane (TAEE)
- hexabromocyclododecane (HBCD) (mixed stereoisomers)
- hydrazine
- manganese
- N-nitrosodimethylamine
- Propylene glycol
- selenium
- toxaphene (weathered)
- 1,2,4-trimethylbenzene (pseudocumene)
- 1,3,5-trimethylbenzene (mesitylene)
- tungsten
- urea
- vandium pentoxide

Chemicals Withdrawn from the IRIS Agenda

- The following assessments are being withdrawn from the IRIS agenda at the request of the EPA Office of Water: aldicarb, aldicarb sulfoxide, and aldicarb sulfone. Assessments of these chemicals will be completed by the EPA Office of Pesticide Programs.

14

SCIENTIFIC CONTENT OF IRIS ASSESSMENTS

15

NAS Risk Assessment Paradigm: Role of IRIS Assessments at EPA

IRIS ASSESSMENT

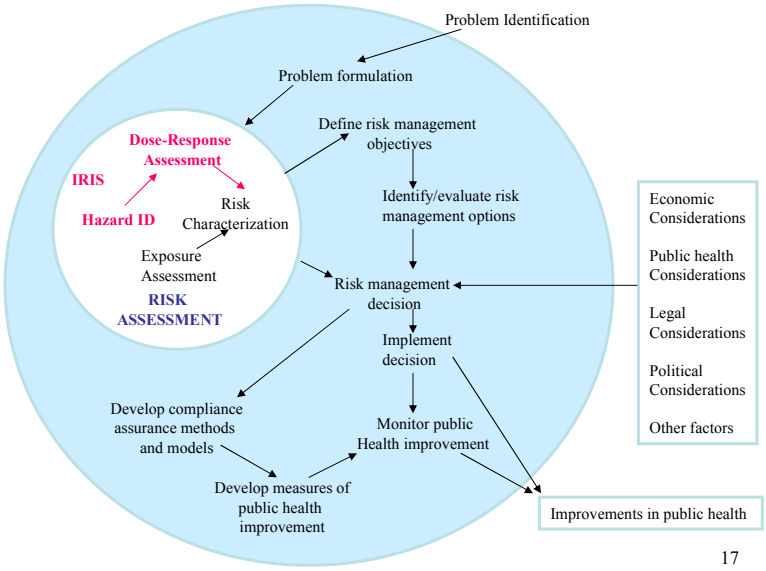
- **Hazard identification: Does exposure cause adverse health effects?**
- **Dose-response assessment: What is the relationship between exposure and incidence and severity of adverse health effect?**

PROGRAM OFFICE OR REGIONAL ASSESSMENT

- **Exposure assessment: What are the intensity, frequency, and duration of exposure of humans to the agent?**
- **Toxicity Values from IRIS assessment**
- **Risk characterization: What is the probability of harm to an exposed individual or population?**

16

The Human Health Risk Assessment-Risk Management Paradigm



17

IRIS TOXICITY VALUES FOR NONCANCER EFFECTS

- **Oral Reference Dose (RfD) (mg/kg-day)**
  - The Oral Reference Dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
- **Inhalation Reference Concentration (RfC) (mg/m^3)**
  - The Reference Concentration (RfC) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

DEVELOPING RfDs and RfCs

- Identify one or more critical studies and effects
- Identify point of departure (points of departure in order of preference from most to least preferred):
  - $95^{\%}$ lower confidence limit on benchmark dose (BMD) (obtained from fitting models to the dataset)
  - No Observed Adverse Effect Level (NOAEL)
  - Lowest Observed Adverse Effect Level (LOAEL)
- Divide Point of Departure by Uncertainty Factors (usually equal to 1, 3, or 10) to account for uncertainties in extrapolation from experimental data and gaps in the database

Uncertainty Factors

- UF_H - to account for variations in susceptible subpopulations
- UF_A - to account for uncertainty in extrapolating from laboratory animals to humans when human data are not available
- UF_S - to extrapolate from subchronic to chronic exposure when a chronic study is not available
- UF_D - to account for database deficiencies
- UF_L - to account for the extrapolation from a LOAEL to a NOAEL, when adverse effects are observed at the lowest dose tested.

Developing Cancer Assessments

- Assign cancer weight of the evidence descriptor
- Identify available key human studies and cancer bioassays
- Attempt to identify carcinogenic mode(s) of action
- Where data are sufficient, select and apply extrapolation methods to develop Cancer Toxicity Value
- If needed, apply Supplemental Guidance for early life exposures

Weight of Evidence Descriptors from EPA Cancer Guidelines

1986 Guidelines	1999 Interim Guidelines	2005 Guidelines
A: Human carcinogen	Carcinogenic to humans	Carcinogenic to humans
B1: Probable human carcinogen (limited human data)	Likely to be carcinogenic to humans	Likely to be carcinogenic to humans
B2: Probable human carcinogen (inadequate or no human data)	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential	Suggestive evidence of carcinogenic potential
C: Possible human carcinogen	Data inadequate for assessment of human carcinogenic potential	Inadequate information to assess carcinogenic potential
D: Not classifiable	Not likely to be carcinogenic to humans	Not likely to be carcinogenic to humans

22

Identify Carcinogenic Mode(s) of Action

- The mode of action is a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. Examples of possible modes of carcinogenic action include mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.

Source: U.S. EPA Guidelines for Carcinogen Risk Assessment.

23

USE OF MODE OF ACTION INFORMATION IN CANCER DOSE-RESPONSE ASSESSMENT

- **Linear extrapolation is used when the dose-response curve is expected to have a linear component below the point of departure**
  - **agents that are DNA-reactive and have direct mutagenic activity, or**
  - **agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process**
- **A nonlinear approach is used when there are sufficient data to ascertain MOA and conclude that it is not linear at low doses and that the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses**
- **Both linear and nonlinear approaches may be used when there are multiple MOAs. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur.**

U.S. EPA Guidelines for Carcinogen Risk Assessment

Cancer Toxicity Values

Linear modes of actions

- **Oral Cancer Slope Factor (CSF):** An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship.
- **Inhalation Unit Risk (IUR):** The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air.

Non-linear modes of action

- **RfD**
- **RfC**

Use of CSF in EPA Risk Assessments

- Risk = dose (mg/kg-day)* CSF (mg/kg-day)$^{-1}$
- Dose is estimated for a specific exposure scenario (e.g., ingestion of a chemical in drinking water or ingestion of a chemical in soil from a contaminated site)
- CSF, as developed in IRIS assessments, is estimated from a database of human and animal studies for a particular chemical and may be combined with dose estimates for any exposure scenario for that chemical
- Risk is expressed as a probability, such as 10^{-4} (1/10,000)

SPECIAL PROJECTS AND NEW DIRECTIONS

IRIS Process Changes Under Consideration

- Enhancements under consideration to identify and resolve scientific issues earlier in the process and involve other federal agencies
- Public release of early draft with qualitative information for technical correction
- More use of early external scientific peer consultation when needed (e.g., NAS)
- Earlier interagency involvement
- IRIS procedures clarified – improved communication
- All recognize importance of rigorous scientific process
- Discussions continuing
- EPA is planning public workshop

External Scientific Engagement

- Scientific peer consultation on issues
- EPA's Science Advisory Board (SAB), National Academy of Sciences (NAS), expert panels used to gain insights on scientific issues
- External peer review of draft assessments
- External (non-EPA) expert panel; often SAB or NAS for major assessments
- Concurrent public comment period
- Public comments made available to reviewers prior to panel meeting
- Disposition of major peer review and public comments provided as appendix to final Toxicological Review

Recent Advances in IRIS Assessment

- Implementation of the EPA Guidelines for Carcinogen Risk Assessment and Supplemental Guidance
- New weight of evidence categories and descriptors
- More emphasis on carcinogenic mode of action and consideration of non-linear MOAs
- Application of age-defined adjustment factors (ADAF) for childhood exposures to chemicals that are carcinogenic by a mutagenic mode of action

Both the final Guidelines and the Supplemental Guidance are available at www.epa.gov/cancerguidelines

Recent Advances in IRIS Assessment

- Benchmark dose modeling
- Increased use of physiologically based pharmacokinetic models
- Establishment of the National Center for Environmental Assessment (NCEA) Pharmacokinetic Work Group (PKWG)
  - Assists in determining whether suitable models are available in the literature for use in IRIS assessments
  - Helps assessors apply models and reviews applications
- Enhanced uncertainty analysis
- Cooperation with Agency for Toxic Substances and Disease Registry (ATSDR) Memorandum of Understanding
- Sharing of literature searches and draft toxicological reviews and profiles; pilot of 1,1,2,2-tetrachloroethane to explore joint development of sections of documents
- Semiannual meetings to review status and assess progress

Important Challenges

- Insufficient MOA information available
- Extrapolation of in vitro data to in vivo systems
- How to incorporate multiple MOAs
- Relevance of animal MOA data to human
- Availability of dose-response information
- Existing and new models

Major Milestones During FY 2007

16 draft assessment submitted to OMB for interagency review

- Acrylamide
- Beryllium
- Carbon tetrachloride
- Cerium and compounds
- Chlordecone (Kepone)
- cis-1,2-Dichloroethylene
- trans-1,2-Dichloroethylene
- Ethylene glycol monobutyl ether (EGBE)
- 2-Hexanone
- Mirex
- Pentachlorophenol
- Propionaldehyde
- Thallium
- Trichloroacetic acid
- 1,2,3-Trichloropropane
- THF

Major Milestones During FY 2007

9 assessments submitted to External Peer Review

- Dibutyl phthalate
- Nitrobenzene
- Bromobenzene
- 1,1,1 trichloroethane
- 1,4-Dichloroebenzene
- Tetrabromodiphenyl ether
- Pentabromodiphenyl ether
- Hexabromodiphenyl ether
- Decabromodiphenyl ether

Major Milestones During FY 2007

2 assessments Posted on the IRIS Web site

- 2,2,4-trimethylpentane
- 1,1,1 trichloroethane

The following 4 assessments will be posted during the next 8 weeks

- Tetrabromodiphenyl ether
- Pentabromodiphenyl ether
- Hexabromodiphenyl ether
- Decabromodiphenyl ether

EPA United States Environmental Protection Agency

Further Information on the IRIS Program

- www.epa.gov/iris - see Recent Additions, Background Documents, and IRIS Track
- IRIS Hotline (202) 566-1676: For questions about IRIS database access and content
- Abdel-Razak Kadry, DVM, Ph.D., DABT, IRIS Program Director (202) 564-1654 or (202) 564-3392

(The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA)

EPA United States Environmental Protection Agency

Thank you very much

Questions, Answers, and Comments

Q. Scott Stoner: Thank you very much for that very comprehensive presentation. I'm really impressed with the numbers of chemicals that are in progress and also your efforts to try to streamline the process. The one thing that I see missing from there that I'd like to recommend is in the nomination process. In the nominations part right at the beginning of your talk, I didn't see any room for state input or state nominations. It is the States that are facing all these emerging contaminants that we need the assessments for that the states can't do individually. Can we add an opportunity so that states can make nominations?

A. Abdel Kadry: Absolutely. The *Federal Register* notice will go to everyone. There are a lot of state-nominated chemicals. In fact, we received 20 nominations so we decided to do the 20 chemicals, and a lot of the 20 nominations were from states. Manganese, for example, was nominated by a state. Then we looked back at the chemical nominations from 2005. We looked back at the chemicals that we did not pick in 2005, and we found that a lot of offices wanted them, so we added the 5, so now we have 25. This year we honor all nominations. I would be more than happy when we have the *Federal Register* notice next year to send an e-mail to all of you as a reminder that we're putting our *Federal Register* notice out. We'd be happy to do that next year.

C. Ambika Bathija: FSTRAC is always communicating with the states, so if you contact us, we can do that for you.

C. Abdel Kadry: Thank you very much.

Q. Helen Goeden: I had a couple of questions on a couple of items that I did not hear mentioned in your talk. It's my understanding that the Risk Assessment Forum is completing a recommendation for harmonizing the way RfDs are derived to other toxicity values, in particular using the body weight raised to three-quarter power in calculations. Are there plans to adopt that once it is finalized?

A. Abdel Kadry: Once it is finalized and it goes through external peer reviews, this will be a document for EPA. Most likely. I don't see any reason not to because we are very open to using the state of the art science

C. Helen Goeden: It was my understanding that it had gone through all the review and was actually in the process of being finalized. My second question is looking at less-than-chronic RfDs. We are incorporating that into our standard development, and for the recent two that IRIS did do, the dibutylphthalate and 1,1,1-trichloroethane (1,1,1-TCA), for both of those examples, it was found that it was less than chronic durations that were actually more limiting. And that is something we are finding that is not unusual in our evaluation. We feel that it is particularly important to try to look at those less-than-chronic durations. Is that something that IRIS will continue?

A. Abdel Kadry: Absolutely. We started a pilot version to do several chemicals—to do acute—but OMB said we could not do acute because the definition of IRIS is a long-term exposure—lifetime—so we cannot do acute. So, we succeeded in 1,1,1-TCA to have less than lifetime, and OMB was okay with that. We did not have anyone tell us not to do it, so we will continue doing it.

Q. Gloria Post: Thank you for your talk. You mentioned and as you know, there is a lot of concern among states about how long the assessments take because of the complexity of the process. How long would you say is the range of what an assessment should take, like between a more straightforward chemical and a very complex one?

A. Abdel Kadry: Small chemical, I would say 2 to 3 years. Big chemical, the sky's the limit. For example, we started working on formaldehyde, and then it came from nowhere that they said we need more scientific data for formaldehyde. So the National Cancer Institute (NCI) has been funded a large amount of money to do studies on the carcinogenicity of formaldehyde. We have been waiting for the assessment from NCI for about 3 years now.

Q. Gloria Post: Really, as you know, for any chemical that someone would want to talk about, you could always say more research could be used probably. Is there any thought of putting something out and then saying that when this study is done we will look at it and update it? Because there is some value to doing something and not waiting, too long, sometimes, I think.

A. Abdel Kadry: You are completely right. We did that for the cancer assessment of beryllium. It is now in interagency review. We were waiting for NIOSH to come up with new study since about 2001. In the end we decided to just go ahead and go forward, and if the NIOSH study comes, we can always go ahead and implement it. But sometimes, for something like formaldehyde, if there is $2 million spent with NCI to do a new cancer study, we have to wait. It becomes a very big thing.

Q. Gloria Post: Do you have any information or any thought on finalizing the assessment for MTBE?

A. Abdel Kadry: That is a very good question. MTBE currently is in a stage of Agency Review. It went through two rounds of Agency Review, and the Agency reviewers still have some issues with it. When it is finished with Agency Review, it will go to OMB Interagency Review. If it survives that, it will go through extended peer review. I cannot give you a time, but we're working on it.

C. Abdel Kadry: I'm sorry I took all of your time.

Q. Ambika Bathija: Dr. Kadry, will you be around for a little while?

A. Abdel Kadry: Yes.

C. Ambika Bathija: Maybe you all can ask him questions later.

C. Abdel Kadry: Please call me anytime at 202-564-1645.

C. Ambika Bathija: Thank you, Dr. Kadry. Let's take a 10-minute break, and we can reconvene at 11:15 a.m.

Current Research and Testing Activities in the National Toxicology Program

Scott Masten
Environmental Toxicology Program, NIEHS
(919) 541-5710
masten@niehs.nih.gov

Visuals follow. Please contact the speaker for more information.

The National Toxicology Program (NTP; http://ntp.niehs.nih.gov) maintains several interrelated research, testing, and evaluation programs that provide unique and critical information needed by health regulatory and research agencies to protect public health. In its chemical testing program, the NTP conducts comprehensive toxicological studies in rodent models to evaluate a variety of human health related endpoints. This program addresses substances of current and emerging public health concern as well as current environmental health and risk assessment issues. Substantial effort is also devoted to the development and application of new methodologies for predictive toxicology including toxicogenomics, biomarkers, life stage and genetic susceptibility, and high throughput screening (HTS) approaches. Studies for the NTP testing program come largely from an open and transparent nomination solicitation and review process. Nominations are received from federal agencies, the public, and other interested parties. The nomination review and selection process is accomplished through the participation of scientists within the NIEHS, other federal agencies, the NTP Board of Scientific Counselors and the public. Substances considered appropriate for study generally fall into two broad yet overlapping categories: (1) substances judged to have high concern as possible public health hazards based on the extent of human exposure and/or suspicion of toxicity and (2) substances for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks, e.g., by facilitating cross-species extrapolation or evaluating mechanisms of toxicity or dose-response relationships. Examples of complex research programs currently underway include toxicological studies of brominated flame retardants, perfluorinated compounds, endocrine disruptors and nanoscale materials. With the continued development of *in vitro* HTS assays targeting toxicologically relevant cellar and molecular responses, large numbers of chemicals can be tested to develop bioactivity profiles. Such bioactivity information together with computational approaches will be useful in prioritizing chemicals lacking sufficient hazard information for *in vivo* toxicology studies.

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Current Research and Testing Activities in the National Toxicology Program

Scott A. Masten PhD, DABT
NIEHS/NTP

Federal-State Toxicology And Risk Analysis Committee (FSTRAC) Meeting

October 18, 2007

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Outline

- What is the NTP?
- Brief overview of testing program
- Study nomination and selection process
- Highlights of recent and ongoing studies
- New testing directions and research initiatives

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NTP Mission

- Coordinate toxicology testing programs within the Department of Health and Human Services
- Strengthen the science base in toxicology
- Develop and validate improved testing methods
- Provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public

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What is the National Toxicology Program?

- Established 1978 in DHHS
- Core Agencies
  - NIEHS, NCTR, NIOSH

- Six other agencies participate through advisory interagency committees
- Research, testing, evaluation, outreach
  - GLP-compliant contract testing
  - Intramural research
  - Public health evaluations
    - Center for the Evaluation of Risks to Human Reproduction
    - Report on Carcinogens
  - Validation of alternative methods
  - Workshops and symposia

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NTP Research and Testing Program

- Open, cooperative, peer review, public data availability
- Toxicological studies of agents, issues, concepts
- 10-20 new nominations formally reviewed each year
- Multiple types of studies per nomination
  - General tox, carcinogenicity, immuno-, neuro-, repro-, developmental, respiratory, genetic, ADME, HTS, *C. elegans*

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What does the NTP study?

- Substances considered appropriate for study generally fall into two broad yet overlapping categories:
  - Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
  - Substances for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks, e.g. by facilitating cross-species extrapolation or evaluating dose-response relationships.
- Input also sought for the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances.

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150+ Substances in Planning, Conduct, Reporting Phase

Areas of emphasis

- DNA-Based products
- Endocrine disruptors
- Herbals/dietary supplements
- Complex occupational exposures
- Phototoxicity
- Green chemistry
- Radiofrequency radiation (cell phones)
- Persistent environmental contaminants
- Drinking water contaminants
- Nanoscale materials
- Toxicogenomics
- Biomolecular Screening

Recent NTP Publications

NTP Technical Reports:

TOX 72: Toxicity Studies of Sodium Dichromate Dihydrate

TR 525: Toxicology and Carcinogenesis Studies of 2,3,4,7,8-Pentalchlorodibenzofuran (PeCDF)

TR 526: Toxicology and Carcinogenesis Studies of a Mixture of TCDD, PeCDF, and PCB 126

TR 531: Toxicology and Carcinogenesis Studies of a Binary Mixture of PCB 136 and PCB 118

TR 534: Toxicology and Carcinogenesis Studies of Divinylbenzene

TR 535: Toxicology and Carcinogenesis Studies of 4-Methylimidazole

TR 538: Toxicology and Ca of Methyl Isobutyl

Available at:
http://ntp.niehs.nih.gov/go/n

NTP Technical Report:

TR 537 *Toxicology and Carcinogenesis Studies of Dibromoacetic Acid*

Genetic Modified Model Report:

GMM 5 Toxicology and Carcinogenicity Studies of Bromodichloromethane in Genetically Modified Mice

Available at:
http://ntp.niehs.nih.gov/go/reports

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How many substances studied?

- 2415 substances tested
  - 2081 single chemical compound
  - 155 defined mixture or formulation
  - 146 undefined mixture
  - 27 macromolecule
  - 6 unspecified/multiple

http://www.epa.gov/ncct/dsstox/sdf_ntpbsi.html

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NTP Technical Reports Peer-Reviewed 2006-2007

- Sodium Dichromate Dihydrate (TR 546)
- Formamide (TR 541)
- Ethinyl Estradiol (multigenerational) (TR 547)
- Ethinyl Estradiol (bioassay) (TR 548)
- Cumene (TR 542)
- Cresols (TR 550)
- Propargyl Alcohol (TR 552)
- Allyl bromide (GMM 7)
- Benzene (GMM 8)
- Dicyclohexylcarbodiimide (GMM 9)
- Glycidol (GMM 13)
- Phenolphthalein (GMM 12)
- Genistein (multigenerational) (TR 539)
- Genistein (bioassay) (TR 545)
- α-Methylstyrene (TR 543)
- Methylene Blue Trihydrate (TR 540)

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Nominations to the NTP's Testing Program

http://ntp.niehs.nih.gov/go/nom

- Formal open process for soliciting and reviewing nominations for new toxicology studies
- Anyone can nominate a substance or issue to the NTP for study
  - Current areas of research
    - http://ntp.niehs.nih.gov/go/current
  - Description of NTP study types
    - http://ntp.niehs.nih.gov/go/type
- Formal review steps
  - NIEHS and Interagency committee reviews
  - NTP Board of Scientific Counselors review
  - Public comment period

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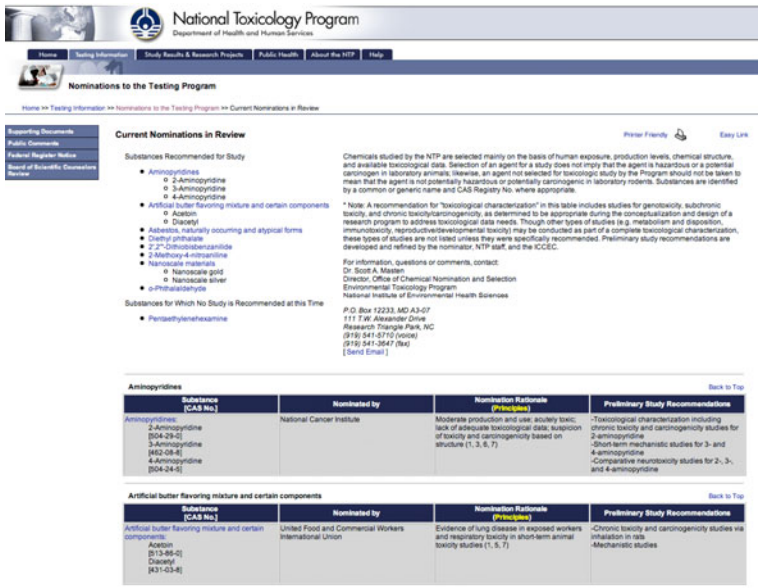
National Toxicology Program
Department of Health and Human Services

Home | Testing Information | Study Results & Research Projects | Public Health | About the NTP | Help

Nominations to the Testing Program

Home >> Testing Information >> Nominations to the Testing Program >> Current Nominations in Review

Supporting Documents
Public Comments
Federal Register Notice
Board of Scientific Counselors Review

Current Nominations in Review

Printer Friendly | Easy Link

Substances Recommended for Study

- Aminopyridines
  - 2-Aminopyridine
  - 3-Aminopyridine
  - 4-Aminopyridine
- Artificial butter flavoring mixture and certain components
  - Acetoin
  - Diacetyl
- Asbestos, naturally occurring and atypical forms
- Diethyl phthalate
- 2,2'-Dithiobisbenzanilide
- 2-Methoxy-4-nitroaniline
- Nanoscale materials
  - Nanoscale gold
  - Nanoscale silver
- o-Phthalaldehyde

Substances for Which No Study is Recommended at this Time

- Pentaerythrenehexamine

Chemicals studied by the NTP are selected mainly on the basis of human exposure, production levels, chemical structure, and available toxicological data. Selection of an agent for a study does not imply that the agent is hazardous or a potential carcinogen in laboratory animals; likewise, an agent not selected for toxicologic study by the Program should not be taken to mean that the agent is not potentially hazardous or potentially carcinogenic in laboratory rodents. Substances are identified by a common or generic name and CAS Registry No. where appropriate.

* Note: A recommendation for "toxicological characterization" in this table includes studies for genotoxicity, subchronic toxicity, and chronic toxicity/carcinogenicity, as determined to be appropriate during the conceptualization and design of a research program to address toxicological data needs. Though other types of studies (e.g. metabolism and disposition, immunotoxicity, reproductive/developmental toxicity) may be conducted as part of a complete toxicological characterization, these types of studies are not listed unless they were specifically recommended. Preliminary study recommendations are developed and refined by the nominator, NTP staff, and the ICCEC.

For information, questions or comments, contact:
Dr. Scott A. Masten
Director, Office of Chemical Nomination and Selection
Environmental Toxicology Program
National Institute of Environmental Health Sciences

P.O. Box 12233, MD A3-07
111 T.W. Alexander Drive
Research Triangle Park, NC
(919) 541-5710 (voice)
(919) 541-3647 (fax)
[Send Email]

Aminopyridines — Back to Top

Substance [CAS No.]	Nominated by	Nomination Rationale (Principles)	Preliminary Study Recommendations
Aminopyridines: 2-Aminopyridine [504-29-0] 3-Aminopyridine [462-08-8] 4-Aminopyridine [504-24-5]	National Cancer Institute	Moderate production and use; acutely toxic; lack of adequate toxicological data; suspicion of toxicity and carcinogenicity based on structure (1, 3, 6, 7)	-Toxicological characterization including chronic toxicity and carcinogenicity studies for 2-aminopyridine -Short-term mechanistic studies for 3- and 4-aminopyridine -Comparative neurotoxicity studies for 2-, 3-, and 4-aminopyridine

Artificial butter flavoring mixture and certain components — Back to Top

Substance [CAS No.]	Nominated by	Nomination Rationale (Principles)	Preliminary Study Recommendations
Artificial butter flavoring mixture and certain components: Acetoin [513-86-0] Diacetyl [431-03-8]	United Food and Commercial Workers International Union	Evidence of lung disease in exposed workers and respiratory toxicity in short-term animal toxicity studies (1, 5, 7)	-Chronic toxicity and carcinogenicity studies via inhalation in rats -Mechanistic studies

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Factors considered in evaluating study nominations

- No quantitative ranking
  - Diverse substances and issues appropriate for study
  - Primarily subjective measures: public health concern, regulatory need, data adequacy
- Extent of known or anticipated exposure to workers, consumers, and the general population, including sensitive subpopulations
  - Commercial production and use patterns; releases to the environment; potential for bioaccumulation/biopersistence; occurrence in environmental media, indoor environments, food, drinking water, and consumer products; human exposure studies and surveys including biomonitoring
- Availability and adequacy of existing toxicological or health effects data
  - Suspicion of toxicity based on structural similarity to a known toxic substance(s) or from existing animal or human studies; availability of sufficient data to reasonably evaluate or predict toxicity [acute, chronic/cancer, reproductive/developmental, immune, neurological, pulmonary]; potential to leverage relevant existing data or complement planned or ongoing similar testing in the U.S. and internationally

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Factors considered in evaluating study nominations

- Extent of stakeholder and/or public concern
  - Specific local, state or federal government needs or public concerns
- Utility of additional studies for public health guidance and/or regulatory decision-making
  - Will additional information reduce uncertainties in risk assessment; will it lead to new regulations or public health guidance, a broader knowledge about the toxicity of substances or classes of substances, a better understanding of the strength of existing or new testing methodologies, or development of predictive toxicology models?

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Sources of Nominations

- "Active" need or concern from external sources
  - Toxicological data to fill knowledge gaps and support regulatory or public health decision-making
- "Passive" screening
  - Occurrence, exposure, or hazard-based
  - Structural features associated with carcinogenicity
  - Product/use classes
  - Literature
  - HPV, CERCLA Priority List, NHANES
- Benefit from "prioritization" work of other agencies/organizations
  - NTP Centers
  - EPA IRIS, ATSDR Priority Data Needs, WHO/IPCS

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Identifying Emerging Contaminants

- Occurrence and exposure information needed to justify hazard studies/testing
  - And vise versa?
- Reliance on research scale and broader monitoring studies
- New toxicological approaches allow early bioactivity screening of emerging contaminants
  - Before broader, e.g. regional or national scale monitoring or exposure studies undertaken
- Need help in bringing emerging contaminants and issues to our attention
  - Communicating findings, even unpublished work and tentative identifications

Water Analysis: Emerging Contaminants and Current Issues

Susan D. Richardson

National Exposure Research Laboratory, U.S. Environmental Protection Agency, Athens, Georgia 30605

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NTP Studies on PFCs and PBDEs

- Perfluorinated compounds
  - Nominated by U.S. EPA 2003
  - Class study to evaluate influence of chain length and functional groups on kinetics, toxicity
    - C4, C6, C8, C9, C10, C12 sulfonates
    - C6, C8, C9, C10, C12 carboxylates
    - 8+2, 10+2 telomer alcohols
  - *In utero*, perinatal and juvenile pharmacokinetic studies on 8 PFCs
  - *In vitro* studies of cellular and molecular effects of 19 PFCs
  - 28-day oral toxicity and developmental toxicity studies (from GD-6 to PND-70) of C6, C8, and C10 carboxylates and sulfonates and 8+2 telomer
  - *In utero* carcinogenicity studies of PFOA
- Polybrominated diphenyl ethers
  - Nominated by CalEPA 1999
    - Penta-BDE and octa-BDE mixtures; BDE-47, 99, 153
  - Subchronic toxicity, *in utero* chronic toxicity/carcinogenicity sudies for Penta-BDE mixture
  - ADME studies on BDE-47, 99, 153 congeners completed

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Water Disinfection By-Products

- Nominated by AWWA Research Foundation and EPA Office of Water 1991, 1995, 1997
- 20 DBPs evaluated
  - Halomethanes, haloacetic acids, haloacetonitriles
  - Chlorate, bromate, MX, cyanogen chloride, chloramine, bromopicrin
- 19 DBPs studied
  - Genetic toxicity, reproductive and developmental toxicity, immunotoxicity, chronic toxicity/carcinogenciity
  - Earlier gavage carcinogenicity studies
    - Bromoform, BDCM, chloroform, CDBM
  - 6 DBPs tested in “conventional” chronic drinking water studies
  - 3 DBPs tested in drinking water studies in genetically modified mice

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DBPs: Recent and Upcoming Reports

- Conventional Toxicology and Carcinogenesis Studies
  - TR-517 Sodium Chlorate, December 2005
  - TR-532 Bromodichloromethane, February 2006
  - TR-537 Dibromoacetic Acid, April 2007
  - TR-544 Dibromoacetonitrile, expected peer review February 2008
  - TR-549 Bromochloroacetic acid, expected peer review February 2008
  - Bromodichloroacetic acid, chronic in progress
- Toxicology and Carcinogenesis Studies in Genetically Modified Mice
  - GMM-05 Bromodichloromethane, May 2007
  - GMM-06 Sodium Bromate, March 2007
  - GMM-11 Dichloroacetic Acid, April 2007

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NTP Studies: Other Drinking Water Contaminants

- CCL1 nominations
  - Aluminum complexes
  - Organotins
    - Dibutyltin dichloride ADME studies
  - Cyanobacterial toxins
    - Cylindrospermopsin
      - Difficulty in acquiring sufficient test material
    - Microcystins
      - Toxicogenomic study planned
- CrVI
  - Michelle Hooth presentation October 19
- Tungsten
  - Sodium tungstate dihydrate
  - ADME studies complete
  - Chronic toxicity study with *in utero* exposure planned

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NTP Nanotechnology Safety Initiative

- Rice University nomination 2003
- NTP workshop on Experimental strategies
  - University of Florida, November 2004
- Identify key components that govern nanomaterial safety
  - Evaluate a cross-section of size, surface coatings, and physico-chemical properties
  - Use these as model nanomaterials for extensive toxicological evaluations
  - Combination of in vitro, ex vivo, in vivo models
- Examine how nanomaterials enter, travel through, and deposit in the body
  - Develop and apply appropriate methods to measure nanomaterials in tissues
  - Discover key attributes that govern intake, deposition, and elimination
  - Develop predictive in silico models.

http://ntp.niehs.nih.gov/go/nanotech

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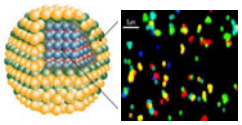
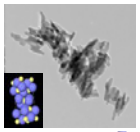
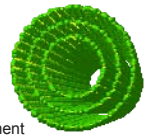
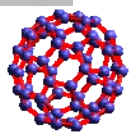
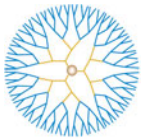
Current Nanoscale Materials Studies



- Quantum dots; Pharmacokinetic studies
  - Impact of surface chemistry
- Titanium dioxide; Dermal pharmacokinetics, and photo-cocarcinogenicity
  - Impact of coatings and crystal state
- Carbon based fullerenes; Pulmonary and oral toxicity
  - Impact of size of aggregates
- Single walled carbon nanotubes
  - NIEHS-NIOSH interagency agreement for inhalation toxicity
- Nanogold
  - Nomination from FDA, review by BSC Dec 2007
- Nano silver
  - Nomination from FDA, review by BSC Jun 2007, project in development
- Dendrimers; Pharmacokinetics and biocompatibility
  - MOU signed with NCIs Nanotechnology Characterization Laboratory
  - Impact of size and surface chemistry
- Ceric oxide
  - Nomination and concept approved- in development



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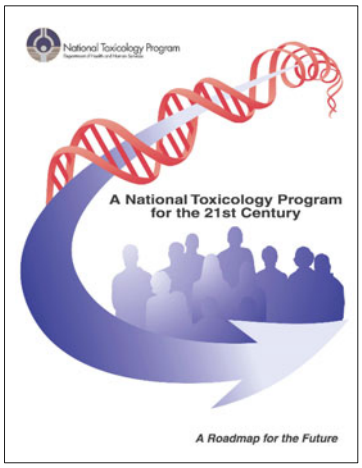
NTP Roadmap

- Refine traditional toxicology assays.
- Expand and evaluate the use of mechanistic and shorter term assays for hazard identification.
- Improve overall utility of NTP products for public health decision-making.



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Roadmap Workshops

- Strains and stocks: Should we switch? June 16-17, 2005
- High Throughput Screening Assays, December 14-15, 2005
- Hormonally-Induced Reproductive Tumors: Relevance of Rodent Bioassays, May 22-24, 2006
- Biomarkers for Toxicology Studies, September 20-21, 2006


NTP Workshop: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains—Should We Switch?


Workgroup Report: National Toxicology Program Workshop on Hormonally Induced Reproductive Tumors—Relevance of Rodent Bioassays


FORUM
Inclusion of Biomarkers for Detecting Perturbations in the Heart and Lung and Lipid/Carbohydrate Metabolism in National Toxicology Program Studies

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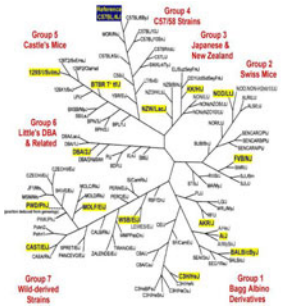
Program Changes in Response to Workshops

- Maintain use of B6C3F1 hybrid mouse
- Discontinue use of F344 rat- select Wistar Han
  - Low incidence of most spontaneous tumors
  - Long lifespan, moderate size
  - Robust reproductive capacity
  - Adequate commercial availability- good colony management
- Reconsider young adult rodent as default model
  - Increased emphasis on children's environmental health and regulations
  - Focus on rat for increased consideration for perinatal dosing
  - Development of draft study design for in *utero*, lactational exposure



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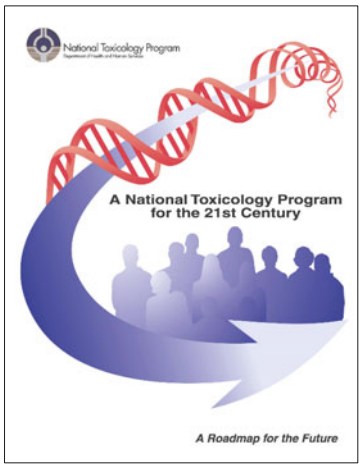
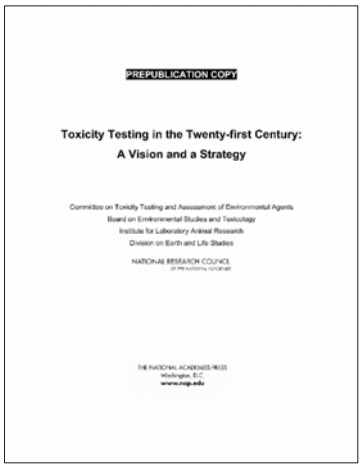
New toxicology testing directions



November 2004



June 2007

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To meet the challenges of 21st century toxicology, the NTP Roadmap includes a major initiative to develop a high throughput screening (HTS) program with 3 main goals:

- Prioritize chemicals for further in-depth toxicological evaluation
- Identify mechanisms of action
- Develop predictive models for in vivo biological response

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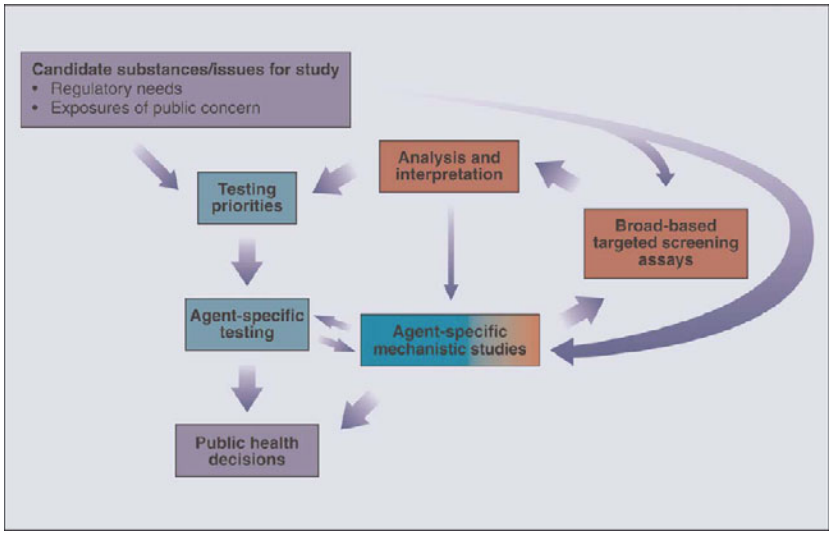
Use of mechanistic and screening studies in public health decision-making



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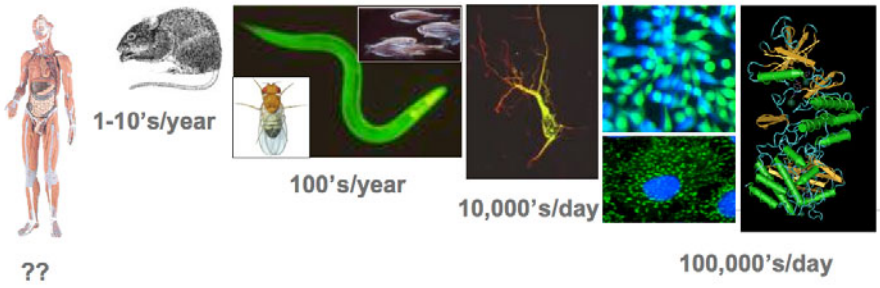
Biological levels and hazard evaluation strategies



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High-throughput screening initiative

- NTP became a formal participant in the NIH Molecular Libraries Initiative (MLI; http://www.mli.nih.gov) in 2005
  - The MLI – a part of the NIH Roadmap for Medical Research – develops and applies automated screening methods to identify small molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways.
  - Generate information that can link data on the biological activity of environment substances with toxicity endpoints identified in the NTP's toxicology testing program
- The NTP assembled a set of 1408 compounds
  - All have pre-existing toxicity data from traditional *in vitro* and/or *in vivo* tests
  - Includes solvents, fire retardants, preservatives, flavoring agents, plasticizers, therapeutic agents, inorganic and organic pollutants, drinking water disinfection byproducts, pesticides, and natural products
  - Selection was based on availability and solubility in DMSO, while avoiding excessive volatility and hazard
- The NTP "1408" have been assayed in 14-pt dose response curves in:
  - Cytotoxicity assay (CellTiter-Glo®; viability) in 9 human and 4 rodent cell types
  - Apoptosis assay (Caspase-Glo® 3/7) in 6 human and 3 rodent cell lines
  - Cytotoxicity assay (Cytotox-ONE™; LDH release) in 1 human and 1 rodent cell line

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Future HTS plans

- Running the 1408 in approximately 60 assays including cell signaling, DNA repair, Hsp90 interactions and other biological activities
- Developing a second set of 1408 chemicals
  - IRIS, Carcinogenic Potency, and HPV databases
  - Focus on compounds tested for a specific toxicological endpoint
- Identifying existing MLI assays specifically focusing on immunotoxicity and cancer
- Continue to collaborate with EPA in the development of ToxCast
- Interpretation
  - Relationship to *in vivo* data
  - QSAR analysis
- And after that:
  - Structural classes based on toxicological interest, metabolites, mixtures

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Host Susceptibility Program

- Mechanism for the planning, conduct and analysis of assessments of chemical toxicity in multiple murine strains
- Short-term studies to examine genetic basis for differences in susceptibility
  - Known toxicants identified in prior NTP long-term studies
- Partnerships with intramural and/or extramural scientists for identification of specific genes that confer sensitivity or resistance to a given toxic agent, and ultimately for an understanding of the key genes and pathways involved in responses to chemicals

NTP
National Toxicology Program

Request for Information (RFI): Genetic variation and the basis for individual susceptibility to environmental toxicant associated disease

- In general, what are the utility and limitations of using model organisms (e.g. multiple strains of isogenic mice, heterogeneous mouse stocks, etc.) to investigate and establish the genetic determinants of biological response?
- Are there particular environmental toxicants associated with human disease where this research approach is immediately applicable and useful to the identification of causally related genes and their allelic variants?
- Similarly, are there particular physiologic or pathogenic pathways and/or disease endpoints for which the proposed research approach is likely to be especially insightful in advancing our understanding of gene-environment interactions?
- What computational, statistical, and bioinformatic methodologies might be particularly useful for determining toxicity phenotypes and identifying associated genes, pathways, and networks?
- What high-data content technologies, platforms, and statistical approaches might be particularly valuable and critical to elucidating the genetic basis for toxicity and disease based upon the experience and knowledge gained over the past decade?
- Are there high-throughput assays and screens using cell-based systems that might be employed to examine the role of genetic variation in human exposure?
- Are in vitro and in vivo assays and genetic models for functional validation of genes useful in permitting orthologous human genes and their allelic variants to be identified and tested in large-scale human populations with defined environmental exposures?
- Is the competitive research partnership approach described for the Host Susceptibility Program using NTP R&D expertise in toxicology and contract resources viable and of general interest to researchers interested in these questions? Why or why not?
- Are there specific concerns over intellectual property or research collaboration issues in a research partnership that should be addressed and negotiated?

http://ntp.niehs.nih.gov/go/32130

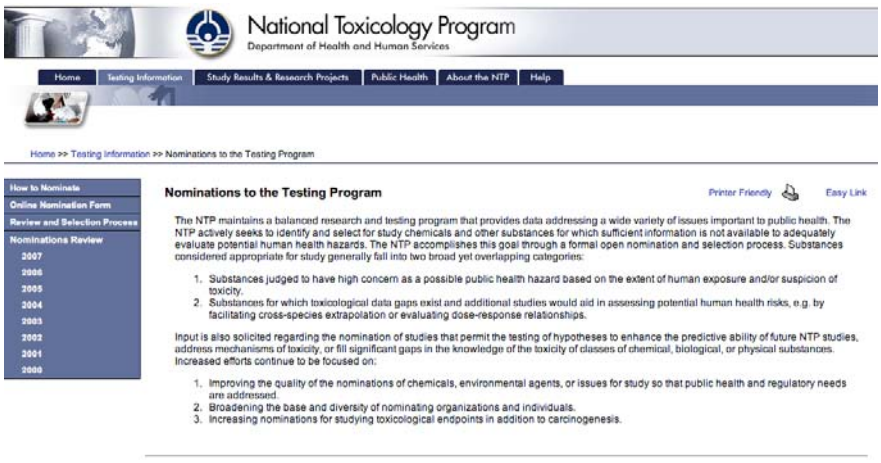
NTP
National Toxicology Program

Program Goals Going Forward

- Continue to provide basic toxicology information for public health protection
- Increase emphasis on understanding and explaining exposure-response relationships and genetic determinants of response
- Integrate results from new “data rich” techniques; genomics, proteomics, HTS screens with existing testing information
- Develop new methodologies for toxicological assessments
- Provide guidance for the proper utilization of new types of information in hazard identification, characterization and regulation

NTP
National Toxicology Program

http://ntp.niehs.nih.gov/go/nom



NTP
National Toxicology Program

NTP Email Updates

- News, website updates, new publications, meeting announcements
- http://ntp.niehs.nih.gov/go/231

NTP
National Toxicology Program

Program Contacts

- Study nominations
  - Dr. Scott Masten, masten@niehs.nih.gov
- Data and reports
  - Central Data Management, cdm@niehs.nih.gov
- Perfluorinated compounds and DBPs
  - Dr. Ron Melnick, melnickr@niehs.nih.gov
- Drinking water contaminants
  - Dr. Michelle Hooth, hooth@niehs.nih.gov
- Nanotechnology Safety Initiative
  - Dr. Nigel Walker, walker3@niehs.nih.gov
- Host Susceptibility Program
  - Dr. Jef French, french@niehs.nih.gov
- HTS Initiative
  - Dr. Ray Tice, tice@niehs.nih.gov

Questions and Comments

Questions, Answers, and Comments

Q. Helen Goeden: On the PFC studies that you are doing, could you indicate a timeline at all for some of those studies?

A. Scott Masten: The PFOA in utero carcinogenicity study is designed but not started. A timeline associated with that type of study is normally a 4- to 5-year timeline. The other studies are quicker studies. The pharmacokinetic studies are getting under way, so we would expect data from those in a year to a year and a half. We need the pharmacokinetic data to design the one-generation reproductive studies, so that whole program is still probably 3 to 4 years out.

C. Helen Goeden: I also noted that for the carboxylates, the C6s (the shortest chain you are looking at). Hopefully, if you are staying for my presentation later, in Minnesota we are dealing with significant contamination with the C4 and some with the C5 as well, and unfortunately they are not on your list of PFCs to evaluate. Specifically, I'm talking about PFBA and PFPEA.

C. Scott Masten: The story gets worse, doesn't it? We had PFBS as part of this program, but I'll have to make a note of that.

Q. Perry Cohn: I have a question going back to something discussed by a previous speaker about MTBE. It's been raised perennially here for the last decade or so, and what I'm thinking is that it will be at least another equivalent amount of time. It seemed to me that if NTP actually did another study of that, which I think it has resisted doing, it would probably have solved a lot of the information problem. There is a problem potentially with formaldehyde as a common denominator, both in terms of oral formaldehyde—MTBE and tert-butyl alcohol going through the formaldehyde process and (if I understand it right) maybe aspartame. The common denominator in some of this is that laboratory in Italy that seems to be coming up with all of these interesting positive studies. I think we need a tiebreaker that really focuses on a broad mechanism that may be a common denominator that would help us all focus on what risks are really out there. Certainly, the MTBE levels seem to be declining in ground water, but I know that we've gone for a long time with the states having a lot of communities being very upset because they can read the Internet, too. There seems to be a lot of indication in their minds that the material is carcinogenic and therefore should have a lower Maximum Contaminant Level (MCL). So, it would be very useful. People have always said, "Well, the MCL for MTBE and tert-butyl alcohol are just around the corner." I've lost hope that they'll ever be just around the corner unless we have another piece of information.

A. Scott Masten: I appreciate that comment. We have looked at MTBE several times over the past decade and, as you've said, we've always made the decision to not do anything based on [the fact that] someone else was doing work and so forth. We've studied tert-butyl alcohol. One of the biggest problems is differences that we've seen in our Program, in studies of many kinds of volatiles, between gavage and drinking water. The Italian studies were by gavage. One of our DBPs was carcinogenic at several sites by gavage. When we did it by drinking water, there was no evidence of carcinogenicity. [That is] one of the other reasons we hesitated to do a drinking water carcinogenicity study of MTBE.

Q. Patrick Levallois: I would like to have some information about the disinfection by-products recent studies, especially the use of genetically modified mice. Why do you use those mice in comparison with conventional carcinogenicity studies? For instance, bromodichloromethane:

You had a report in 2006 with traditional conventional studies, and in 2007 a recent report with genetically modified mice. What is really the added value of those studies?

A. Scott Masten: It was bromodichloromethane that I was just referring to, where we performed carcinogenicity studies by gavage some years ago and it was positive, and in the most recent drinking water carcinogenicity studies, it was negative. And it was negative as well in two kinds of genetically modified mice. All those studies or reports are available or the abstracts are on the Web, and I could also directly extract that information and send it to you. I'll do that.

Q. Ambika Bathija: You spoke about comparing gavage and drinking water studies. Do you get the same dose with drinking water studies with animals? With gavage you can give the dose you want, but in drinking water sometimes if the animals don't like the taste, they don't drink the water.

A. Scott Masten: A lot of times in our drinking water studies, part of our workup is palatability studies to see at what level the taste becomes intolerable to the animals, which means they don't get enough water, which is a compromised study. That is an issue. There is a great discussion in that bromodichloromethane technical report about the differences between the gavage and drinking studies.

Q. Ambika Bathija: So, you think that they are valid studies?

A. Scott Masten: Yes, it was quite perplexing to us. We can't fully explain what the differences are. But Ron Melnick, one of the scientists leading those studies, I'm sure could give you some of his thoughts. It wasn't purely a dose or kinetic issue.

C. Ambika Bathija: Because this bromodichloromethane you are talking about, I thought the dose by drinking water was lower than the dose given by gavage.

C. Abdel Kadry: Regarding the Italian lab, 3 months ago we had a meeting between EPA, NTP, and FDA. There was a very honest discussion at the meeting about the carcinogenicity results coming from the Ramazzini group and whether they should or should not be used. The scientific community is completely divided. Some scientists say it is completely valid data, while others say it is a bad lab with no quality assurance and so on. We're planning to have a big meeting to discuss this particular issue. It's a big issue. With some major studies, it may be that the only carcinogenicity-positive studies are coming from this particular lab.

Q. Perry Cohn: There is a question of how long the dosing continued—if the animals survived and they kept giving them additional doses. The flipside might be if they started dosing at earlier ages. Would you actually see an effect and then, ultimately, is this really a linear effect or is it a threshold effect?

A. Abdel Kadry: It's a big issue. Some people will come back and say that this is a normal exposure for a lifetime. It's really like we spend the whole day discussing this. Each side's argument is really strong. That is why I think we should have a big meeting, almost like a public meeting, to address this issue.

Q. Perry Cohn: Are you saying that the public meeting will have these discussions potentially published as opposed to the meeting you just had?

A. Abdel Kadry: It will be a public scientific meeting. Yes, the meeting we just had was a very limited meeting. But we hope to invite people from academia, industry, other federal agencies, states, and from the Ramazzini Foundation itself to come and talk about the issue. It is a big issue, and we have a lot of data in the literature. In the meeting we had 3 months ago, some people visited the lab. The scientific community is very divided.

C. Perry Cohn: That's not news.

Q. Ambika Bathija: We can continue this discussion later. I'd like to thank Dr. Masten. We have a choice. We can take a lunch break, and when we come back I can give my presentation. Or maybe I can give it later on. What is the consensus? Do you want to take a lunch break, or do you want to continue?

A. Audience: *The audience members said they wanted to take a lunch break.*

C. Ambika Bathija: Let's come back in an hour and reconvene at 1:00 p.m.

OST/HECD/OW Update

Ambika Bathija
U.S. Environmental Protection Agency
(202) 566-1087
Bathija.Ambika@epamail.epa.gov

Visuals follow. Please contact the speaker for more information.

HECD/OST/OW Update

FSTRAC Meeting
October 17 - 19, 2007
RTP, NC

Ambika Bathija, Ph.D.
US-EPA, Washington, DC

Office of Science and Technology
OD: Ephraim King

- Engineering & Analysis Division
- Standards and Health Protection Division
- Health and Ecological Criteria Division
  - Ecological and Health Processes Branch
  - Ecological and Risk Assessment Branch
  - Human Health and Risk assessment Branch
    - Toxicology
    - Microbiology

Human Health Risk Assessment Branch
BC: Elizabeth Doyle

- Contaminant Candidate List (CCL)
- Six Year Review of NPDWRs
- Arsenic, Atrazine, Fluoride, PPCPs, ECs
- Microbiology Activities
- DBPs

Contaminant Candidate Lists (CCLs)
(Joyce Donohue)

- 1996 SDWA - EPA must make regulatory determinations for at least five contaminants every five years
- CCL 1: July 18, 2003 (8 chemicals & 1 microbial agent)
- CCL 2: In April 2004, draft CCL 2 was published as CCL 1 minus 9 previously regulatory determination contaminants from CCL 1

Regulatory Determination for CCL2
(contd)

Federal Register (May 1, 2007) – EPA made preliminary regulatory determinations for 11 of 51 CCL 2 contaminants:

-Boron, dacthal degradates(2) 1,3-dichloropropene, dinitrotoluenes (2), DDE, EPTC, fonofos, 1,1,2,2-tetrachloroethane, terbacil.

-Health advisories updates proposed for boron, dacthal and its degradates, 1,3-dichloropropene, dinitrotoluenes, 1,1,2,2-tetrachloroethane.

- Fact sheet for utilities on cyanobacteria and their toxins.

CCL 2 Regulatory Determinations Comments and Status

- Comments (from ~ 10 individuals/organizations)
  - Request for extension of the comment period.
  - Support for the 11 negative determinations.
  - One requested reason for not making determination on CCL2 chemicals not discussed in the notice.
- Status of final determinations
  - Preparing final FR notice.
  - Preparing Response to Comment Document.
  - Expect to publish ~ mid-2008.

CCL 3

- Process for selection of CCL contaminants developed and subjected to expert review
  - Follows NRC and NDWAC Recommendations
  - Broad universe of chemicals evaluated from over 39 data sources (including chemicals listed on CCL 1 and CCL 2)
  - Chemicals nominated by public included in Universe
  - Screened Universe to a Preliminary CCL for further review
- PCCL chemicals scored for health effects (potency, severity) and occurrence (prevalence and magnitude)
- Applied trained decision algorithms (3) to PCCL
- Selected draft CCL3
- Draft Federal Register Notice and CCL3 at OMB
- Proposal anticipated in 2008

Six Year Review of NPDWRs

(Nancy Chiu)

1996 SDWA - review & revise existing NPDWR every 6 years, if appropriate.

- **1st Six Year Review results published on July 18, 2003**
  - Reviewed 69 NPDWRs
  - Decided to revise Total Coliform Rule
  - Other 68 NPDWRs (for chemicals) still considered appropriate

Six Year Review of NPDWRs
(contd.)

- **2nd Six Year Review**
  - Evaluating 73 NPDWR (other NPDWRs have been or are being addressed under separate regulatory efforts e.g. Lead and copper, DBPs, LT2)
  - Statutory deadline for final results is mid-2009
  - Key components of the review include an evaluation of any new health assessments, occurrence data, analytical methods and treatment technologies
  - Among the 73 chemicals, 26 chemicals are under current OW or IRIS or OPP or NAS risk assessments
  - HECD started literature search for the remaining chemicals for possible reproductive, developmental and other health effects updates.

Six Year Review of NPDWRs
(contd.)

Activities Related to Health Effects of Regulated Contaminants

- Chromium – NTP completed bioassay on Cr (VI) in drinking water. Pathology report on NTP website. EPA will review Final NTP report due 2007
- Lead – EPA preparing HA and a white paper on the toxicokinetics. The toxicokinetic data will be used in modeling the impact of lead from drinking water on blood lead levels. The toxicokinetic projections will be incorporated in the HA
- Fluoride
- Inorganic Arsenic

Fluoride(Joyce Donohue)

- NAS Report published in March 2006
- NAS concluded MCLG for fluoride should be lowered
  - **Severe dental fluorosis is an adverse health effect because it decreases the protective function of enamel**
  - **MCLG may not be protective for bone fractures**
- NAS Recommendations:
  - **Conduct a quantitative health risk assessment for the noncancer endpoints of concern**
  - **Consider the cancer endpoint after ongoing Harvard Cancer studies are published**
  - **Collect data to establish a Relative Source Contribution (RSC) for drinking water**
- Status
  - **Draft EPA noncancer assessment in internal review**
  - **Second Harvard study not yet published**
  - **RSC analysis initiated**
    - **OGWDW has collected updated monitoring data from utilities**

Inorganic Arsenic
(Santhini Ramasamy)

- Science Advisory Board Report on EPA's IRIS cancer assessment was released in June 2007. SAB recommendations include continuing the linear approach and compare the risk estimates with other epidemiological studies. Agency is revising the cancer assessment.
- For the non-cancer assessment, Agency is reviewing new data from Bangladesh population published in 2006 after completion of which the assessment will undergo external peer review.
- Separate IRIS documents on cancer and non cancer assessments are scheduled for completion in Spring 2008 and 2009, respectively.
- The AWQC will be developed after completion of the human health assessment.

Atrazine - Drinking water Health Value

(Amal Mahfouz)

- OW and OPP coordinating risk assessment for atrazine. IRED published on October 31, 2003
- Science Advisory Board meeting took place in July 2003 to peer review epidemiological data on prostrate cancer at atrazine manufacturing plants. A decision was made that additional assessment is needed for this effect**.**
- In 2006 OPP published Cumulative Risk for Triazine – atrazine, simazine & propazine. OW will use this document in the 6-year review and CCL process.
- Oct. 9 – 12 SAP is meeting to determine the final position on atrazine reproductive/developmental effects on frogs. The report is due in 30 – 60 days
- OW is including atrazine in the 6-yr review; decision to update MCLG/MCL will be forthcoming in 2008

Pharmaceutical & Personal Care Products Emerging Contaminants

(Octavia Conerly)

- Assessing information on occurrence, health and ecological effects in water as a critical step for prioritizing ECs for possible 304(a) criteria development
- Working to pinpoint sources of occurrence, develop standardized analytical methods & determine effectiveness of various treatment technologies
- Working with other Federal Agencies, White House IA-WGs on Pharmaceuticals and EDs in the Environment, and various stakeholders to better understand the problems.
- July 18, 2007 EPA launched the PPCPs website- www.epa.gov/ppcp - for the general public and scientists.

Pharmaceutical & Personal Care Products Emerging Contaminants (contd.)

Continuing several studies to enhance knowledge:

- PPCP Fish Tissue Pilot Study. Analytical results available late this year
- Study of POTWs to characterize occurrence of historical and new pollutants, emphasizing ECs, in effluents and sludge. Interim results expected late 2008
- National Sewage Sludge Survey (biosolids) –sampling over 50 pharmaceuticals, steroids & hormones. Results expected late 2008.

Microbiology Activities

(Stephen Schaub)

Microbial Risk Assessment (MRA):

- Thesaurus of MRA terms/definitions now on OST web
- Initiated effort to establish MRA protocol for use in AWQC setting
- Will update draft MRA protocol for water media

Risk Assessment Forum MRA Activities (reports are available at EPA Risk Assessment Forum Website):

- Developed MRA Risk Communications Guidelines report
- Report of Colloquium on Immunotox. and life stage impacts on Immunity to enteric disease pathogens
- Co-lead for Interagency working group to establish cross-agency MRA guidelines (with USDA, DOD, Homeland Security)
- Comprehensive analysis report of MRA framework for use in designing future EPA MRA guidelines
- Presenting another Colloquium on Interagency MRA Guidelines development at Society of Risk Analysis in San Antonio – Dec 2007

Microbiology Activities
(contd.)

Recreational Water Program:

- Recreational Water Program

  - Participated in Expert workshop to define R&D needs for future 304(a) recreational water criteria (Airlie, VA) Workshop report Available on EPA Web Site

  - Participated in development of "critical path" recreational water Science Plan for EPA – draft document

  - Initiated literature based studies to determine "state of science" on recreational water indicators/pathogens:

    > regrowth/survival of fecal indicators in tropics and impacts on relevance to Criteria development

    > compare disease risks for animal borne pathogens versus same pathogens in humans

    > determine cross-species infectivity of zoonotic pathogens

Drinking Water Health Advisories& Standards

- The Health Advisories and Standards table was updated in October 2006 and is available on the Internet under the Health Advisories Heading on the OST Home Page. The table also includes OPP values updated in August 2006. www.epa.gov/waterscience

Ecological & Health Processes Branch

BC: Bill Swietlik

Areas covered by the Branch

- Biosolids regulations/risk assessments
- Nutrient criteria development
- Biocriteria & TALU

Biosolids Regulatory Update

- History
- Response to NRC report
- Summary of 14 projects
- Future directions

Biosolids – History

Rick Stevens

- Pertinent biosolid regulations
  - CWA Section 405
  - 40 CFR 503
- Biennial reviews of Part 503 are required by the CWA
- As a result of Congressional hearings in 2000, EPA requested an independent study from the NAS-NRC

Biosolids – History

contd.

- In 2003, EPA received a petition from the Center for Food Safety
  - -Petition asked for moratorium on land application of biosolids based on health risks
  - -Denied: unsubstantiated claims
- NAS report was issued in July 2002
- In 2003, EPA announced its decision not to regulate dioxins in land-applied biosolids (www.epa.gov/waterscience/biosolids)

Biosolids
Response to NRC Report

- In July 2002 NRC published: "Biosolids Applied to Land: Advancing Standards and Practices" Report recommended actions to address public health concerns, uncertainties and data gaps in science in the sewage sludge standards.
- In response to NRC Report EPA developed a strategy that was signed on 12/31/03 and published in the FR on 1/8/04
  - Included 14 project action plans and results of a biennial review of additional chemicals for possible regulation in biosolids
  - Through these and other activities, EPA will continue to address the protectiveness of standards for use and disposal of biosolids

Biosolids
Summary of 14 Projects

Projects responding to NRC Report:

1. Biennial Review under the CWA
2. Compliance Assistance and Enforcement Actions
3. Methods Development for Microbial Pollutants
4. Field Study of Application of Sewage Sludge
   Targeted National Survey
6. Participate in an Incident Tracking Workshop
7. Conduct and Exposure Measurement Workshop
8. Assess the quality and utility of data, tools and methodologies to conduct microbial risk assessments

Biosolids (contd.)

Projects Responding to NRC Report (contd)

9. Support the Pathogen Equivalency Committee
10. Development of Analytical Methods for Detecting PPCPs
11. Publish Proceedings of USEPA-USDA Workshop
12. Support "S*ustainable Land Application*" Conference
13. Review Criteria for Molybdenum
14. Improve Stakeholder Involvement

Eight projects completed

Biosolids

Future Directions

- **Short term activities**
- Comply with 405(d)(2)(C)
- Complete the survey and applied activities
- Validate new methods as developed
- Evaluate how current activities inform other research

- **Long term additional Needs**
- Further development of microbial test methods
- Evaluate potential exposure to individuals near biosolids land application sites
- Microbial risk assessment methodology
- Incident tracking and investigation
- Evaluate potential risks from emerging compounds – (e.g. prions, PPCPs, nanomaterials)

Nutrient Criteria Update

Steve Potts

- History
- Current Status
- Future Directions

Nutrient Criteria History

- June 1998 National Nutrient Strategy outlined EPA's goals *to develop Waterbody Type Technical Guidance Manuals and Ecoregional Nutrient Criteria for all water body types*
- EPA committed to supporting States/Tribes in developing their own nutrient criteria
- 2001 Policy memo presented expectations and flexibility for States/Tribes

Nutrient Criteria
(contd.)

What has EPA produced;

- Four Technical Guidance Manuals:
  - Lakes and reservoirs (2000)
  - Rivers and Streams (2000)
  - Estuaries and Coastal waters (2001)
  - Wetlands – in progress

  - A statistical (distribution based) approach to develop estimated ecoregional reference conditions
    - 26 documents with estimated ecoregional reference conditions for lakes, reservoirs, rivers, and streams (2001-2).

Nutrient Criteria
(contd.)

- A Technical support system which:
  - Allows states to pose questions to national nutrient experts;
  - Provides advanced statistical analysis of state water quality data;
  - Provides hands-on workshops on topics such as statistical techniques for effects-based nutrient criteria development, preparing water quality standards packages, and methods for sampling chlorophyll and periphyton.

Nutrient Criteria
Current Status of State Plans

- 50 States and Territories have Plans
- 29 are mutually agreed upon
- About 80% of States are using a cause and effect approach to develop criteria
- About 20% are using statistical approaches
- 21 States have committed to adopting standards by 2008; 26 by 2010

Nutrient Criteria (contd)

- Implementing a Nutrient strategy focused in 4 areas:
  - Implementation support to states close to adopting criteria;
  - Technical support to states still in the process of calculating draft criteria;
  - Develop criteria methodologies for wetlands and large rivers, and case studies describing how to develop criteria for selected wetlands, estuaries, coastal waters;
  - Improve public outreach on nutrient problems.
- Continue financial support to States to help them adopt numeric criteria

Nutrient Criteria
Future Directions

- The nutrient and bio-criteria programs were merged into the same branch as of October 1, 2007.
- Discussions are beginning to determine how to provide states with the best scientific and technical support for implementing both programs.

Ecological Risk Assessment Branch
BC: Joe Beaman (acting)

- Areas covered by the Branch:
  - Criteria Development
    - Aquatic Life
    - Human Health
  - Aquatic Life Guidelines Revisions
  - ESA National Consultation Issue

Criteria Development

- Develop Ambient WQC to protect designated uses under §304(a)(1) of the Clean Water Act
- Use Criteria Selection Process – consistent with Problem Formulation process under both the 1998 ERA Guidelines and the Aquatic Life Criteria Guidelines

Current Criteria Underway

- Atrazine
  - Recent SAP for amphibian gonadal development studies (October 2007)
  - SAP for CASM Model (December 2007)
  - Proposed Release – late 2008 w/ implementation guidance
- Selenium
  - Bluegill "Overwintering" study underway
  - Finalize conclusions in December 2007
  - Proposed Release – late 2008 w/ implementation guidance
- Acrolein
  - Current – Review of OPP risk assessment
  - Proposed Release – late 2008
- Ammonia
  - Current – re-evaluating need for criteria based on protection of T&E mussels – numerous stakeholder letters

New Criteria "Starts"

- Pesticide Criteria Scoping Assessments
  - Metolachlor
  - Acetochlor
  - Carbaryl
- Based on possible EDC activity, stakeholder interest – AAPCO-SFIREG and others
- EDC Case Study – chemical TBD

Human Health

- Chloroform
  - Completed; waiting on release of Exposure Assessment TSD
  - Final in 2009
- BAF TSD
  - Final Late 2008
- Exposure Assessment TSD
  - Final

Aquatic Life Guidelines Revisions

- New Committee Chair – Joe Beaman
- Recent Activities
  - Criteria Duration and Frequency TSD
  - Pellston Workshop – Tissue Based Criteria
  - Water Quality Criteria Derivation Methodology for Emerging Contaminants (Revisions Committee workgroup)
- Upcoming Near Future
  - Full Committee Re-engagement – November 2007
  - SAB Consultation EC criteria derivation methodology

ESA National Consultation Issues

- Recent Activities
  - CN Formal Consultation with Services
  - ESA Regional Consultation Strategy Template

POC's

- Atrazine, Acrolein – Frank Gostomski
- Selenium – Charles Delos
- Ammonia – Lisa Huff
- Pesticides – Luis Cruz
- Human Health – Heidi Bethel
- Aquatic Life Guidelines – Joe Beaman
  - 202-566-0420
  - Beaman.joe@epa.gov

Questions, Answers, and Comments

C. Ambika Bathija: My handout is in the back. If there are any questions or comments, ask me or my Branch Chief, who is here. Maria Gomez-Taylor, our Deputy Division Director, is also here and she can also answer some of your questions.

Q. Connie Brower: Is EPA's *Water Quality Criteria Derivation Methodology for Emerging Contaminants* out yet?

A. Maria Gomez-Taylor: It is not out yet, but it should be coming out shortly.

Q. Connie Brower: Is that to be used in conjunction with the new way that they are looking at 303(d) listings and 305(b)?

A. Maria Gomez-Taylor: Yes.

C. Connie Brower: I think sometimes that it would have been helpful to have had that document out before somebody was judging us on whether we were meeting our standards. That sort of put the cart before the horse. That is what we are dealing with.

A. Maria Gomez-Taylor: It has been in review for quite a while. Also, something that should be noted is that the *Wetlands Nutrients Manual* was just signed. I think it is on our Web site now. Ambika showed it as being in progress, but it has actually been completed.

Overview of ATSDR Activities for PFOA

Clement Welsh
Agency for Toxic Substances and Disease Registry
(404) 498-0448
clement.welsh@cdc.hhs.gov

Visuals follow. Please contact the speaker for more information.

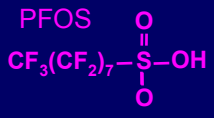
Overview of ATSDR Activities for PFOA

"The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy."

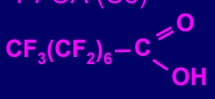
Polyfluoroalkyl chemicals

- Persistent environmental chemicals produced since 1950's
  - Surface treatments
  - Paper protection
  - Performance chemicals
- Persistent chemicals in humans
  - Half-life in humans is several years
  - Distribute mainly to liver and serum
  - Bind to plasma proteins
- Adverse health effects in experimental animals
  - Liver damage
  - Developmental toxicity
- Limited data in humans

PFOS



PFOA (C8)



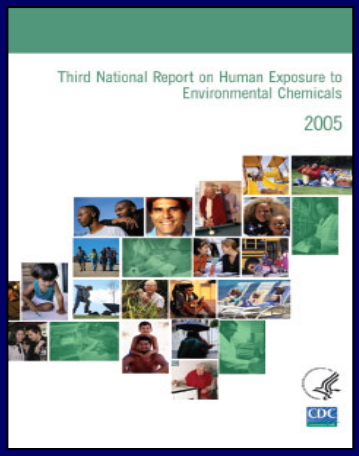
Potential sources of PFCs

- Packaging materials
  - Food contact
- Stain-resistant coatings on textiles, carpet & leather
- Fire fighting foams
- Pesticides
- Contaminated drinking water
- Degradation products

CDC

Third National Report on Human Exposure to Environmental Chemicals

- 148 chemicals in blood and urine
- Approximately 2400 people
- Nationally representative sample
- More then 350,000 measurements
- Years: 2001-2002 and includes previous data from 1999-2000



www.cdc.gov/exposurereport

CDC

PFCs in NHANES

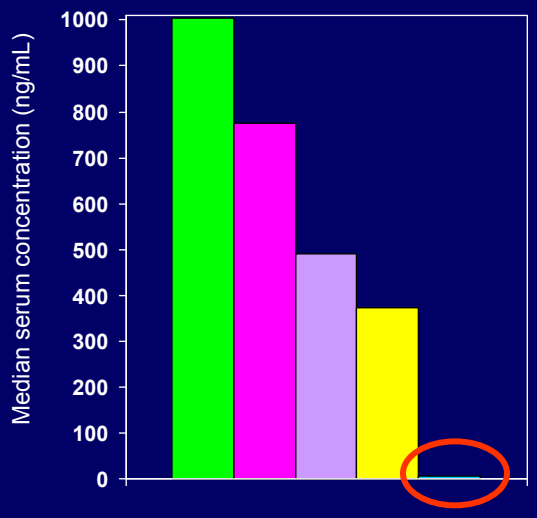
- **11 PFCs were measured in 1562 people (12 years of age and older)**
  - **Representative of the general US population**
  - **Demographics: sex, age & race/ethnicity (Mexican-American, non-Hispanic white, non-Hispanic black)**

Calafat et al. ES&T 2007, 41:2237-2242.

Findings – NHANES

- Seven PFCs were detected in more than 90% of samples
  - PFOS > PFOA > PFHxS
- Variability in the prevalence and magnitude of exposure to PFCs
  - Unlike other POPs, most PFCs do not show clear "age" trends
    - Most pronounced at younger ages
  - Mexican Americans have the lowest concentrations
  - PFOA and PFOS concentrations are higher in males than in females.
  - Higher education associated with greater concentrations of PFOS and PFOA

Comparing PFOA Levels



- Occupational (N = 6; SD = 2642 ng/mL; Ehresman et al. Environ. Res. 2007)
- Occupational (N = 18; IQR= 422-999 ng/mL; Emmett et al. JOEM 2006)
- Occupational (N = 259; US EPA Public Docket AR-226-1922 2005)
- Little Hocking water system (N = 291; IQR = 221-576 ng/mL; Emmett et al. JOEM 2006)
- NHANES 1999-2000 (N = 1562; 95% CI = 4.7-5.7 ng/mL; Calafat et al. ES&T 2007)

CDC

Historical Involvement with PFOA

Advisors on various state projects (prior to 2004)

PFOA / PFOS workgroup (2004 - 2005)

CDC

Recent Involvement

Request from WV Bureau of Public Health

Questions Posed:

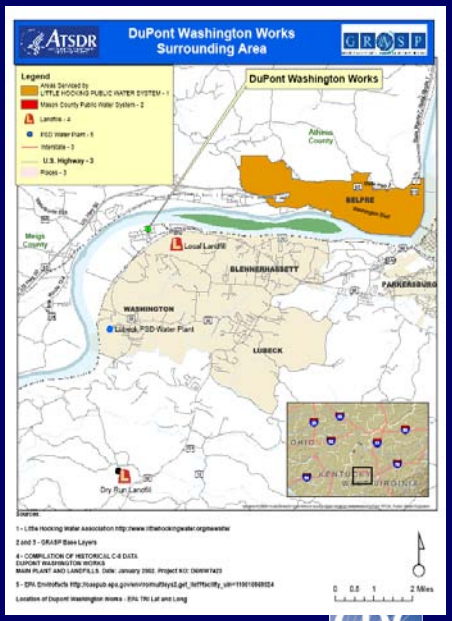
1) **Is their a public health threat posed by continued consumption of water supplies contaminated by PFOA?**

2) **Should infant formula be reconstituted with residential water containing PFOA?**

3) **What are recommendations for follow up health activities for this population?**

DuPont Washington Works Facility

- **PFOA utilized by facility since early 50's**
- **Emissions released in air, discharged to Ohio River, or shipped off-site for disposal**



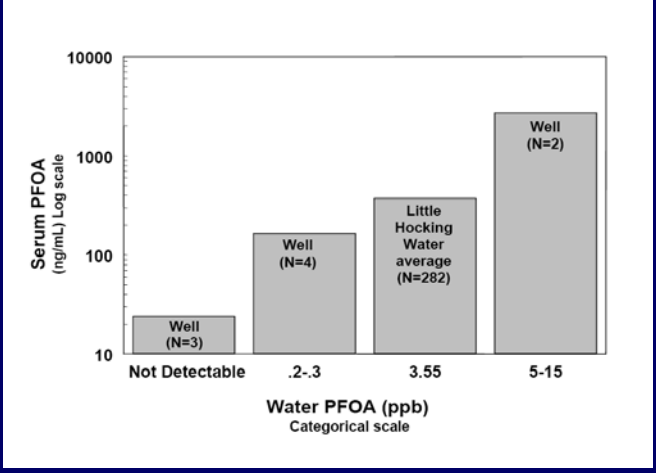
Study by Researchers at the University of Pennsylvania

291 serum levels of PFOA measured on users of a contaminated water supply

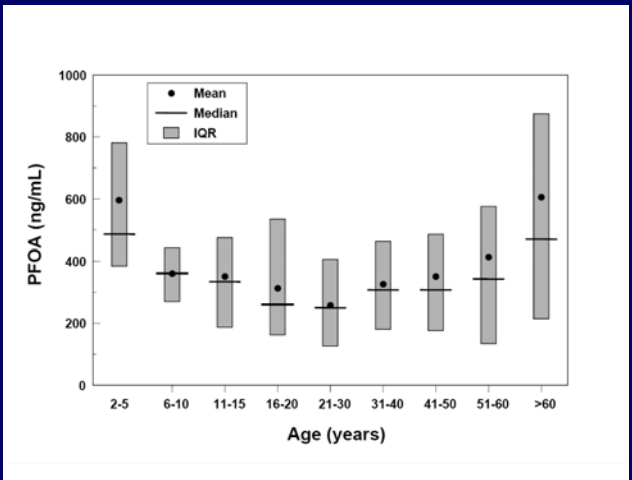
Little Hocking Water System; PFOA = 3.55 ppb (mean for years 2002-2005)

Median serum PFOA concentrations of 374 ng/ml.

Serum PFOA Concentrations vs. Water PFOA Concentrations



Age vs. Serum PFOA



Primary Findings

- **Drinking water appears to the primary exposure pathway.**
- **Older and younger study participants had higher serum PFOA levels than other age groups.**

Primary Findings

- The study found "no significant positive relationships between serum PFOA and liver or kidney function tests, cholesterol, thyroid-stimulating hormone, or with red cell indices, white cell, or platelet counts".
- "Mean serum PFOA was not increased in those with a history of liver disease or thyroid disease".

Primary Findings

- "No toxicity from PFOA was demonstrated using the measured end points; other endpoints need to be addressed."
- "Based on the findings in experimental animals, other endpoints, particularly cancer, reproductive and childhood endpoints require further study."

Data Gaps / Notes

- Extent of contamination in area wells is not known.
- The individual with the highest serum PFOA level was a well water user.
- Well water users (n = 26) showed more variability in serum PFOA levels.
- Follow-up work: aimed at producing a better estimate of the PFOA half-life in humans.

C-8 health Project

Part of a class action lawsuit settlement
>64,000 serum samples with questionnaires

Aims of the project:
- determine health effects of C-8 exposures
- direct additional toxicity studies
- identify most impacted groups

Reassurance from:

- Occupational epi studies show only subtle, if any clinical changes.
- No significant changes from clinical norms in the Emmett cohort
- “Background levels” in humans are well below effect levels in test animals.
- Cancer-related mechanisms found in test animals may not apply to humans.

Anxiety from:

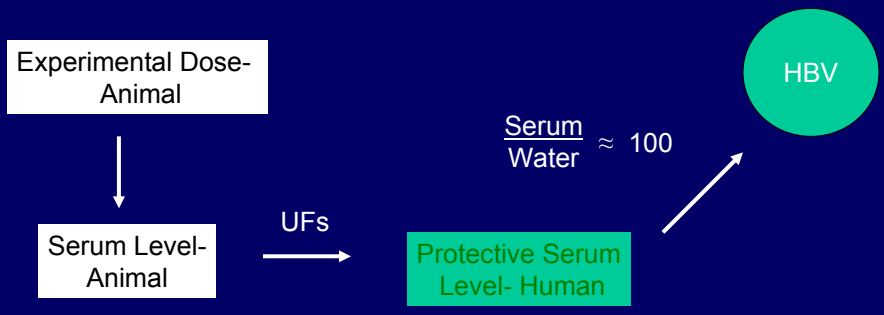
- “Sensitive indicators” may be reproductive / developmental effects.
- Placental transfer of PFOA occurs.
- Variability in different test species; longest half-life is in humans.
- Youngest and oldest folks with highest levels.

Pharmacokinetic Differences

- Physiologic half-life for PFOA
  - Rats:
    3 - 16 hrs (female)
    138 - 202 hrs (male)
  - Monkeys: 21-33 days
  - Humans: ~ 4 yrs

Derivation of Health-Based Values

Derivation of Health-Based Values



Ongoing ATSDR Activities

- **Working to complete the Health Consultation for West Virginia.**
- **Contributing to community and physician education.**
- **Working to develop a "chemical specific" health guidance.**
- **Continuing to monitor research developments and will update advice as needed**

Questions, Answers, and Comments

Q. Gloria Post: I was really interested in your talk because I used a similar approach for drinking water guidance that I'm going to present later in this session. As I understand it, when the health study with the 70,000 people is done, part of the data will include the blood levels of the people and the level in the water that they ingested. So there should be much more data on that ratio than what we have now, I would think.

A. Clement Welsh: That's my impression also. My understanding is that some of what I'll call primarily descriptive data is going to be released in early winter. Some of that reporting of water levels and blood levels is supposed to be among that. There will be some at least preliminary epidemiological treatments of those data. The first results are supposed to be out early in the year. Some of the longer-term studies—for instance, the half-life studies—are supposed to go on for 4 years.

C. Gloria Post: I can't remember what all the studies are off the top of my head, but there are a lot of them and they are really comprehensive.

A. Clement Welsh: There are 10 studies outlined in this C-8 Health Project that came out of a class action suit in West Virginia and Ohio. I can't remember most of them, but I know there is one that will deal with half-life, there is another one with people with birth outcomes, there is one that just looks at the information. They have the medical histories of people that answered questions and try to make an association apparent there. I'm going to say that most are epidemiological in nature, and many will take a number of years beyond this release of the initial data that is what I'm basically calling "descriptive." The bottom line is that the first indications from that study are expected out the first part of next year.

Q. Elizabeth Doyle: Are there indications so far that they have development effects in the area, or is there any sense of that so far?

A. Clement Welsh: To my knowledge, no, but I also can't say that there have been any serious investigations on that.

C. Helen Goeden: Actually, I think the birth outcomes study is going to be one of the studies that will be the longest before they report effects. Cardiovascular, I think, is one of the earlier studies that they are going to report effects for.

Perfluorinated Chemicals: Overview of EPA's Research Activities

Christopher Lau
U.S. Environmental Protection Agency
(919) 541-5097
lau.christopher@epa.gov

Visuals follow. Please contact the speaker for more information.

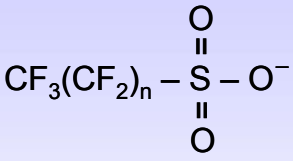
The perfluoroalkyl acids (PFAAs, such as PFOS and PFOA) and their derivatives are important chemicals that have numerous consumer and industrial applications. However, recent discoveries that some of these of compounds have global distribution, environmental persistence, presence in humans and wildlife, as well as toxicity in laboratory animal models, have generated considerable scientific, regulatory, and public interest on an international scale. In support of human and environmental heath risk assessment of these chemicals at U.S. EPA and other regulatory agencies, several laboratories at the Office of Research Development (ORD) have launched research projects to develop analytical methods for detection of PFAAs in the environment as well as in tissue matrices, to investigate the fate and distribution these chemicals in various environmental media, to examine the degradation and release of PFAAs from consumer products, and to evaluate the potential toxicities of these chemicals in laboratory animal models. These multiyear projects involve investigators from the National Exposure Research Laboratory (NERL), the National Risk Management Research Laboratory (NRMRL), the National Health and Environmental Effects Research Laboratory (NHEERL) and the National Center for Computational Toxicology (NCCT). This overview will highlight the findings from these investigations, and the current research activities. This abstract does not necessarily reflect US EPA policy.

Perfluorinated Chemicals: Overview of EPA's Research Activities

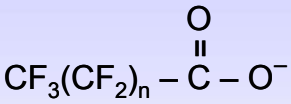
Christopher Lau

Reproductive Toxicology Division
Research Triangle Park, NC

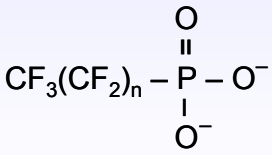
Perfluoroalkyl Acids (PFAA)



Perfluoroalkyl sulfonic acid



Perfluoroalkyl carboxylic acid



Perfluoroalkyl phosphonic acid

What are PFAAs?

- Stable, synthetic chemicals, produced last ~50-60 years
- Their hydrophobic and oleophobic properties make them ideal surfactants (water and oil resistant).
- The most useful PFAAs are the 8-carbon (C8) chemicals:
  Perfluorooctane Sulfonate (PFOS)
  Perfluorooctanoic Acid (PFOA)
- PFOS, PFOA (Telomer Alcohols) and their derivatives have over 200 industrial and consumer applications:

Fabric coatings	Fire-fighting foam
Carpet coatings	Airplane gear lubricant
Paper coatings	Mining/oil well surfactants
Floor polish/wax	Acid rust/dust suppressants
Alkaline cleaners	Metal electroplating
Denture cleaners	Electronic etching bath
Shampoos	Polymer additives
Insecticides (ant/roach)	Emulsifiers for polymer production

PFAAs Commonly Found in the Environment

- Perfluorooctane Sulfonate (PFOS, C8)
- Perfluorooctanoic Acid (PFOA, C8)
- Perfluorononanoic Acid (PFNA, C9)
- Perfluorohexane Sulfonate (PFHxS, C6)
- Perfluorohexanoic Acid (PFHxA, C6)
- Perfluorobutane Sulfonate (PFBS, C4)
- Perfluorobutyric Acid (PFBA, C4)
- Perfluorodecanoic Acid (PFDA, C10)
- 8:2 Telomer Alcohol
- 10:2 Telomer Alcohol

Why should we care about PFAAs?

They are everywhere …

- PFAAs are stable and persistent in the environment
- They are present in water, air, soil, sediment and sludge
- They are distributed globally (from the Artic to the South Pacific)

PFAAs in water ***(ppt)***	**NC** Cape Fear	**TN** Tennessee	**WV** Little Hocking	**Great Lakes**
PFOS *(ng/L)*	132	114	--	21-70
PFOA *(ng/L)*	287	394	3,500	27-50

They are in our body and in wildlife …

(ppb)	PFOS	PFOA	PFHxS	PFNA
NHANES I	**30.4**	**5.2**	**2.1**	**0.5**
NHANES II	**20.7**	**3.9**	**1.9**	**1.0**
Production Workers	1,500 - 2,000	500 - 1,000	~500	--
Children	40.1	5.2	5.3	--
Lake trout	121	4.4	0.6	2.9
Polar bear	~1200	~10	--	~100

They hang around …

Ser. $t_{½}$	PFBS	PFHS	PFOS	PFBA	PFOA
Rat			**100 days**	**2 hrs (f)** **8 hrs (m)**	**2-4 hrs (f)** **6-7 days (m)**
Mouse				**3 hrs (f)** **17 hrs (m)**	**17 days (f)** **19 days (m)**
Rabbit					**7 hrs (f)** **5.5 hrs (m)**
Dog					**8-13 days (f)** **20-30 days (m)**
Monkey	**3-4 days**	**87 days (f)** **141 days (m)**	**150 days**	**1.7 days**	**30 days (f)** **21 days (m)**
Human	**10-20 days**	**8.7 years**	**5.4 years**	**2-4 days**	**3.8 years**

They may be harmful …
(some adverse effects of PFOS and PFOA from laboratory animal studies)

- Hepatotoxicity
- Carcinogenicity
- Immunotoxicity
- Hormone imbalance
- Developmental toxicity

Agency's Concerns of PFAAs

- Where do they come from?
- How do they get into our body? To the wildlife?
- Why do they stay so long in humans?
- How much are there in our body? In the environment?
- Are they harmful? At what levels?
- Are replacement/alternative products to C-8 better?

Activities at EPA OPPTS & Regions

- Toxicological reviews of PFOS by OPPT and OECD in 2002
- Human health risk assessment of PFOA by EPA in 2005 and review by SAB in 2006
- De-listing of perfluoroalkyl phosphonates from inert chemicals by OPP in 2006
- 2006 EPA PFOA Stewardship Program with industry to reduce facility emissions and product contents of PFOA and related chemicals on a global basis by 95% by 2010, and toward elimination by 2015
- Consent order issued to industry by Regions 3 and 5 in 2006 to lower level of PFOA in drinking water from 150 ppb to 0.5 ppb in WV/OH areas

Activities at EPA ORD

- Multiyear research plans in “Safe Pesticides, Safe Products”
- Involvement of multiple Laboratories
  - NHEERL (*Chris Lau/Doug Wolf*)
  - NERL (*Andy Lindstrom/Ross Highsmith)*
  - NRMRL (*Marc Mills*)
  - NCCT (*Hugh Barton*)
- Collaboration between laboratory investigators and scientists from program offices

Activities at NERL I (*Lindstrom and Strynar*)

- Method development for detection of PFAAs
- Detection of PFAAs in water
  - Samples from Cape Fear River basin in NC and Upper Mississippi River basin
- Detection of PFAAs in fish (homogenates, fillet, liver)
  - Samples from N. America: MN, NC, and other states
- Detection of PFAAs in soils
  - Samples collected from U.S., China, Norway, Japan, Greece
- Detection of PFAAs in house dust
- Detection of PFAAs in food
- Detection of PFAAs in breast milk
- Support NHEERL studies for PFAA dosimetry

Activities at NERL II *(Washington)*

- To investigate the distribution of PFAAs in soils and sediments, and factors that may influence these processes
- To examine whether fluorotelomer-based polymer products can degrade to PFAAs in soils and sediments, and to estimate the rates of this process

Activities at NRMRL

(Guo and Fehrenbacher)

- To determine the PFAA content in new consumer products that contain fluoropolymers and/or fluorotelomers
- To determine releases of PFAAs from consumer products by accelerated aging tests and under close-to-realistic exposure conditions
  - 100+ articles covering 22 product categories tested
  - Target compounds include 8 PFAAs (C5 – C12)
  - Analyses and report to be completed by 2008

Activities at NHEERL

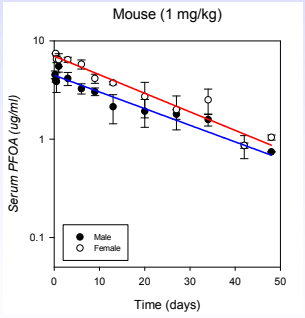
- Characterization of developmental toxicity of PFOS, PFOA, PFBA
- Elucidation of mechanisms of PFAA toxicity
- Evaluation of pharmacokinetic disposition of PFAAs in various rodent models – comparison of chain lengths and functional groups
- Investigation of the modes-of-action for PFAA effects (developmental, hepatic)
- Evaluation of PFAA toxicities by toxicogenomic approaches
- Evaluation of the PFAA immunotoxic potentials

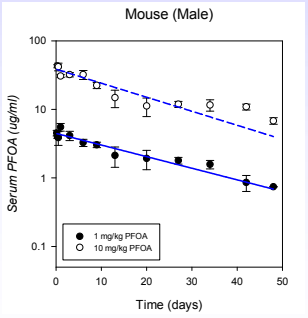
Investigators at NHEERL

- Elaine Francis (*Nat. Prog. Director*)
- Doug Wolf (*Asst. Lab Director*)
- Chris Lau (*Team Lead at RTD*)
- John Rogers (*dev tox, mech. of tox*)
- Barbara Abbott (*dev tox, modes of action*)
- Sue Fenton (*dev tox, long-term impacts*)
- Mitch Rosen (*toxicogenomics*)
- Bob Luebke (*immunotox*)
- Gary Ankley (*reprod tox in fish and frog*)

Pharmacokinetics of PFOA

Species	Dose	Days of treatment	Males	Females
Rat	10 mg/kg	20	111 ± 10 µg/ml	0.69 ± 0.18 µg/ml
Mouse	20 mg/kg	17	199 ± 19 µg/ml	171 ± 15 µg/ml

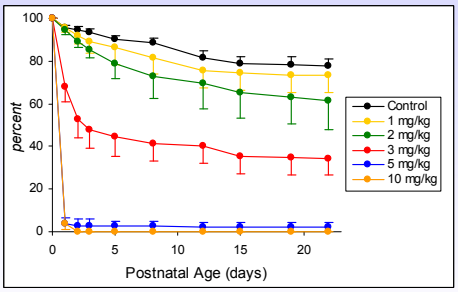




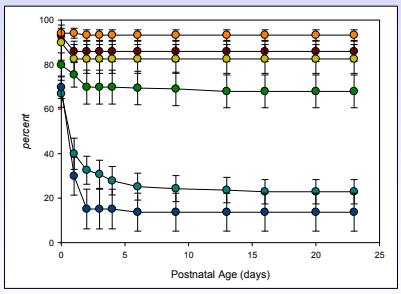
	Male	Female
Half-life (days)	19.1	16.6

Developmental Toxicity of PFAAs

PFOS - Rat



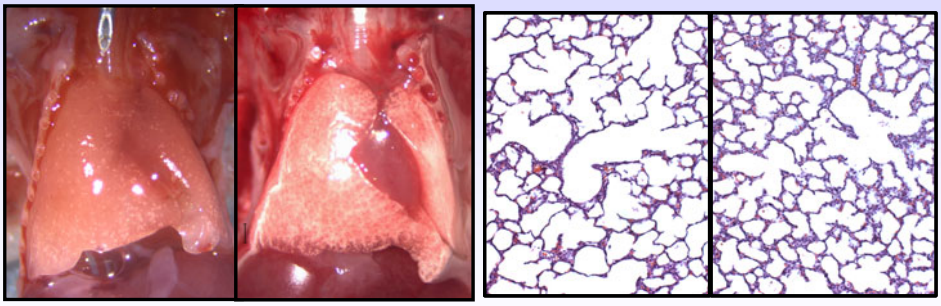
PFOA - Mouse



Percent of surviving pups after in utero exposure

Mechanism of toxicity for PFOS

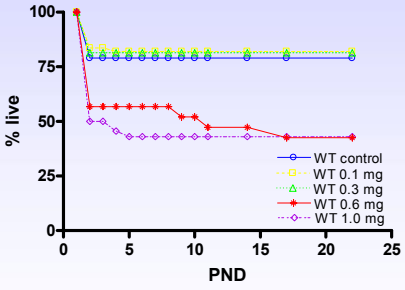
Control **PFOS** **Control** **PFOS**



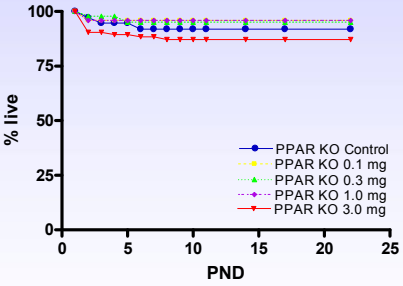
Lungs of newborns after in utero exposure

Mechanism of toxicity for PFOA

Wildtype Mice



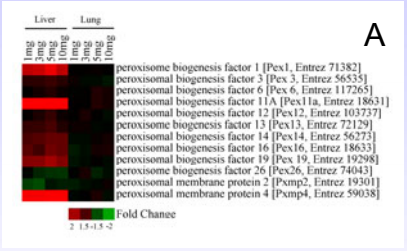
PPARα-null Mice



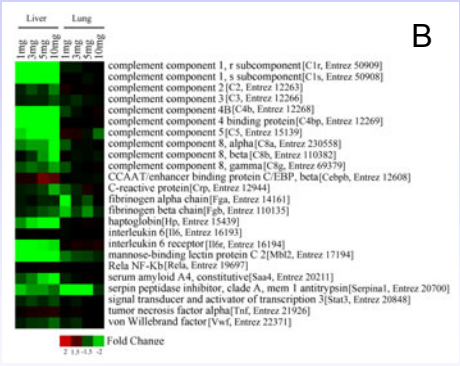
Involvement of PPARα molecular signals

Gene expression in PFOA-exposed fetal liver and lung

A



B



Increased peroxisome biogenesis (A) and down-regulation of inflammatory response (B) were seen in liver but not lung. Changes of genes involving lipid metabolism and transport, cholesterol and bile acid synthesis, glucose, steroid hormone and phospholipid metabolism were also noted in the liver.

Gene expression in liver of newborns

Genes	Functions	Control	PFBA			PFOA
			35 mg/kg	175 mg/kg	350 mg/kg	10 mg/kg
Acox1	PPARα – β-oxid	1.0	-1.6	-1.2	-1.2	3.7
Me1	PPARα - FA	1.0	-1.1	1.1	-1.1	8.5
Peci	PPARα – β-oxid	1.0	-1.1	-1.1	-1.2	3.1
Ehhadh	PPARα – β-oxid	1.0	-1.9	-1.6	-1.8	12.7
C4a	Inflammation	1.0	-1.1	1.1	-1.1	-3.0
Cyp3a4	PXR marker	1.0	1.0	-1.7	-2.3	-10.7
Gadd45b	DNA damage	1.0	-1.6	-1.4	-1.1	3.5
Pdk4	Gluc. metab.	1.0	1.5	-1.4	1.1	7.4
Cyp2b10	CAR marker	1.0	ND	ND	ND	2.0

Activities at NCCT *(Barton)*

- To provide support for pharmacokinetic studies of PFAAs at NHEERL
- To provide physiologically-based pharmacokinetic models for species extrapolation (humans)
- To provide models to account for the long residence of PFAAs (transporter activities, protein binding, renal resorption)

EPA

Health Risk Considerations

- No significant associations between PFOS or PFOA exposure and health problems reported by production workers
- Some concordance between findings in laboratory animals and in humans
  - Placental and lactational transfers
  - Accumulation in liver
- Longer half-lives in humans
  - Persistence may lead to higher body burden
- Margin of exposure
  - Internal benchmark doses only a few hundreds times higher than body burdens in general population, even less so for production workers and selectively exposed populations
  - Humans exposed to a mixture of PFAAs

ORD NHEERL

C. Helen Goeden: Our next speaker is Dr. Christopher Lau. He is a lead research biologist in the Developmental Biology Branch of the Reproductive Toxicology Division at NHEERL here in RTP. His research interests include developmental toxicology, teratology, and risk assessment modeling. He is going to give an overview of EPA's activities related to the PFCs.

Q. Luanne Williams: Thank you. That was an excellent presentation. Based on the modeling that you've done so far with rodents, can you say for the most part that the rodent models, rodent serum levels, and rodent dose-response for particularly the developmental benchmarks in the liver and serum concentration benchmarks—those are probably the two most sensitive benchmarks that we've found in rodents—how relevant are those effects to humans? And would you, at this point, recommend using the primate data for determining an equivalent human serum concentration?

A. Christopher Lau: As of now, I don't have any feel one way or the other. This is why we are studying what is the actual biological basis that drives the species differences in genetics. We know that there are some commonalities. For instance, the liver seems to be a depot. Even at death, there seems to be a trend. It is a more preferred depot in a rodent than in a primate, so the ratio goes from maybe 4:1 in the rodent for the liver-to-serum ratio to maybe 2:1 in the monkeys and maybe 1.5:1 in the human. So, there is a little bit of a trend. What we'd like actually, rather than making guesses, is to see what is driving it. Why is the chemical being transported to the liver? There is some evidence, for instance, of the involvement of the transporter protein that may be transporting it at least in the rodent. So, if we know that that's the only means of storing chemical, then we can go back to humans and see if we have the same amount of transporter protein. Can we actually use that to predict based on the transport of the chemical? These are the kinds of studies that we are launching to get a better handle rather than just making estimates of ratios from this to that and can we apply a corrective factor. I mean, if you don't have any information, I know that's what you have to do today. That's the kind of thing we are working on.

Q. Luanne Williams: So that would be one factor, the carrier protein. What about the peroxisome proliferator-activated receptor (PPAR)-alpha mechanism for the liver and the reproductive and developmental effects in rodents?

A. Christopher Lau: PPAR-alpha is really interesting. I could spend another hour talking about it. This is very relevant to your talk coming up in terms of the additivity of the chemical. A number of these chemicals are PPAR agonists, but their potency is very different. For instance, PFOA is quite a bit stronger agonist than PFOS. Right now, for instance, Barbara Abbott is performing some studies with PPAR knockout animals to see whether you can knock that out and look at PFOS. We are doing a toxicogenomic study to determine how, if PFOS is such a weak PPAR agonist, you get a big liver. There may be other molecular pathways involved. There are actually suggestions that other nuclear receptor-mediated mechanisms are involved. We are just really at the beginning of understanding what the molecular and cellular drivers are, even though when you weigh the livers, they are bigger; but there are many ways to make a liver bigger. By understanding it a little better. On the other hand, C9 and C8 are almost equally strong PPAR agonists. Barbara Abbott has a cell culture study, and what she does is transfactor the PPAR receptor in the cell and then she can just screen through all the chemicals in terms of relative potency of the chemical. That paper should be coming out sometime next year. At least in the cell culture system, she can make predictions.

C. Mark Johnson: Regarding your first bullet on your last slide, I'd offer some caution about the interpretation of no effect in that worker cohort. That's largely a male population and the impacts on what—perhaps a few women that may have been part of that worker cohort may not have actually measured the impact of fetal exposure. The lack of information there may be a somewhat limited interpretation.

C. Christopher Lau: I think 3M is having a paper coming out soon. That is a very good point. To some extent, it is really not their fault. It turns out that they just have a lot more male workers than female workers so they are sort of stuck with what they've got. But they are actually tracking the female workers a little bit better. They will have a paper coming out very soon to again track the female workers in different job categories. They go back and look at the birth weight of the babies and gestation length. The paper is available electronically. The last name of the author is Grice.

Q. Mark Johnson: Did they see any effects in that study?

A. Christopher Lau: They saw no association. At least, that is what they reported.

Q. Mark Johnson: My question is more to do with trying to identify the various potential sources of exposure. Putting aside the West Virginia–Ohio population, do we have any sense from existing data about the major contributors to our intake in the general population—whether it be food, water, fish, ambient air, or whatever? Is there any sense for ballpark estimates?

A. Christopher Lau: It really depends on who you speak to. If you speak to Gloria, she will probably tell you it's from drinking water.

C. Gloria Post: No, no.

C. Christopher Lau: I probably shouldn't put you on the spot. A lot of people have different feelings. I don't have a particular one myself. I think once the manufacturers put in better filters, they can actually reduce the emissions significantly, so you know that has to be part of the equation. How much is actually coming from our consumer products? I don't see many systematic studies on that.

C. Mark Johnson: I was struck by your summary table, where you had fish or lake trout. Being from the Great Lakes, it's one of the aspects that we look at very carefully in terms of a source of exposure. If you just make some crude estimates about consumption, especially of high-consuming populations, that could be a major source of exposure.

C. Christopher Lau: It could be.

C. Gloria Post: It seems like a lot is coming out now that the telomer alcohols, which are much more commonly used than PFOA, are in a lot of consumer products and paper that is used to wrap food. It has been shown that they can be metabolized to PFOA in the body and that they can migrate into the food—and people are exposed to them—and then be metabolized. PFOA doesn't degrade in the environment. It does not degrade, so it might be that for the general population where everyone has about 5 ppb in their blood (not in a place where the water is highly contaminated like West Virginia), a lot of people's exposure to PFOA isn't from PFOA itself because that is not as commonly used, but it is from these other products. So phasing out

PFOA wouldn't solve the problem of exposure of the general population if the other products are still used.

C. Clement Welsh: I just want to add one comment. It is one that I meant to make in my presentation but failed to. The newest NHANES information has the values that Chris pointed out relative to PFOA. The earlier numbers were in the range of 5 ppb, and the newer numbers are in the range of 4 ppb. I think it is important for this discussion and maybe to add some perspective, the 95th percentile from the newest NHANES is about 10 ppb. Surprisingly, that was about 10 ppb for all age groups that were analyzed.

Immediate & Long-term Health Impacts of Prenatal Exposure to PFOA in Mice

Suzanne Fenton
U.S. Environmental Protection Agency, NHEERL
919-541-5220
fenton.suzanne@epamail.epa.gov

Please contact the speaker for more information.

Introduction: Perfluorooctanoic acid (PFOA), an environmentally persistent chemical detected in the sera of humans and wildlife, is a surfactant with wide consumer and industrial applications. PFOA induces tumors of the liver, pancreas, testis and mammary gland in lifetime fed adult rats. Our studies, using the CD-1 mouse model that appropriately mimics the clearance of this compound in humans, investigate the effects of gestational/lactational exposure to PFOA in neonatal and adult offspring. Our early studies using 5 mg/kg PFOA during varied windows of fetal development have demonstrated delayed mammary epithelial proliferation in mouse neonates and mammary alveolar differentiation in adults. Late pregnancy appears to be a critical window of exposure. **Methods:** To evaluate the immediate and long-term health effects of PFOA, pregnant CD-1 mice were given 0.01, 0.1, 0.3, 1, 3, or 5 mg/kg PFOA by oral gavage daily from gestation days (GD) 2-18 (n>30/dose group; except 3 mg/kg) and their female offspring were evaluated until 18 months of age. **Results:** Although the pathological evaluation for tissues of mice dosed with less than 1 mg/kg are not completed, our data from the higher doses (1-5 mg/kg) are available and are presented here. Exposure to PFOA at 5 mg/kg caused about a 20% increase in neonatal mortality within 5 days of birth. Postnatal survival of the offspring improved at lower doses and was not compromised at doses less than 3 mg/kg, but significant growth retardation of pups was noted in the 3 and 5 mg/kg groups. Body weights recovered to the control level by about 6 weeks of age and PFOA-exposed mice continued to gain more weight compared to controls as they aged. This led to dose-related increases in body weight in 18 mo old mice ($p<0.05$, 4-17%), at a time when only background levels of serum PFOA were detectable. At 18 months, gross evaluations revealed a significant ($p<0.05$) dose-related increase in >1mm ovarian cysts visible in 25, 47, 60, and 80% of the animals in the 0, 1, 3, 5 mg/kg dose groups, respectively. An increased incidence of bursal and parovarian cysts was detected in PFOA-exposed animals. In whole mount preparations of the mammary glands, macropscopic examination revealed abnormal hyperplasia in the glands and the number of hyperplastic nodules per affected gland increased with dose. In addition, in PFOA-exposed mice, altered spleen and thymus size were noted and the amount of brown adipose tissue was significantly increased ($p<0.05$), when evaluated using body weight as a covariate. Liver:body weight ratio at 18 mo was similar across groups, but 100% and 25% of PFOA exposed offspring exhibited significant centrilobular hepatocellular hypertrophy and periportal hepatocellular cytoplasmic vacuolization, respectively, upon pathological examination. **Conclusions:** These results suggest that *in utero* and lactational exposure to PFOA may lead to increased adiposity in adulthood as well as abnormalities in a number of endocrine-regulated tissues. *(This abstract does not necessarily reflect EPA policy).*

Questions, Answers, and Comments

Q. Mark Johnson: That was a very good presentation. You mentioned the lactational effects and decrease in body weight gain in the pups. Can you distinguish whether that is because of the diminished nutritional value of the milk or whether it is because of decreased production of milk and they just don't get enough of it?

A. Suzanne Fenton: We'll be able to tell you the answer to that in a year or so. We've done the experiment and collected the samples to be able to do it. We did a fairly extensive study where we actually milked the mice and collected the milk from them over a long period of time, so we would get those answers. I don't know right now. I do know right now that there is more than one altered milk protein in the mammary glands of these animals.

Q. Mark Johnson: You showed that there was no effect at 80 weeks with the liver-to-body weight ratios, yet you saw 100 percent hypertrophy. How do you explain that? Is it because the body weights are so much larger and that the ratio doesn't change?

A. Suzanne Fenton: That's a good question. One of the things that we are doing now is correlations between a lot of the different endpoints, not just simple significance testing. So, I think that will all fall out. I don't have the answer for you right now. We're not sure either. It's possible that the focal areas of hypertrophy that they saw in those sections weren't enough to cause an overall increase in size. So, it was focal. It wasn't like the whole gland was affected. That was true for the vacuolization. It was focal.

New Jersey Health-based Drinking Water Guidance for PFOA

Gloria Post
New Jersey Department of Environmental Protection
(609) 292-8497
gloria.post@dep.state.nj.us

Visuals follow. Please contact the speaker for more information.

Health-based drinking water guidance for PFOA was developed in response to a request from a public water supply with PFOA detections. The starting point for the assessment was the USEPA draft risk assessment (2005) and the Science Advisory Board (2006) review of this assessment. The USEPA draft risk assessment (2005) aimed to evaluate the significance of the exposure of the general population to PFOA and developed margins of exposure (MOEs) in humans compared to LOAELs and NOAELs from animal studies. USEPA (2005) classified PFOA as a suggestive carcinogen, while the SAB (2006) classified it as a likely carcinogen. Since the half-life of PFOA in humans is much longer than in animals, MOEs are based on comparison of animal and human blood levels rather than administered doses. However, USEPA did not address the relationship between intake of PFOA and blood levels in humans, and this information is needed to develop drinking water guidance. A study of an Ohio community ingesting water contaminated with PFOA indicates that there is a 100-fold concentration factor between PFOA in drinking water and blood (e.g. 1 ug/L in drinking water results in 100 ug/L in blood), and this concentration factor was used to develop health-based drinking water concentrations for the non-cancer and cancer endpoints identified by USEPA (2005). The most sensitive endpoints were decreased body weight and hematological effects in a chronic study in female rats, and the guidance value based on this endpoint is 0.04 ug/L. The drinking water concentration based on cancer at the one in one million risk level is 0.06 ug/L. The calculation of the guidance value will be presented and uncertainties will be discussed. The document presenting this assessment is found at http://www.nj.gov/dep/watersupply/pfoa_dwguidance.pdf.

References:

Emmett, E.A., Shofer, F.S., Zhang, H., Freeman, D., Desai, C., and Shaw, L.M. (2006). Community exposure to perfluorooctanoate: Relationships between serum concentrations and exposure sources. Journal of Occupational and Environmental Medicine 48 (8): 759-770.

USEPA (2005). Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and Its Salts. Office of Pollution Prevention and Toxics. January 4, 2005.

USEPA (2006). SAB Review of EPA's Draft Risk Assessment of Potential Human Health Effects Associated with PFOA and Its Salts. May 30, 2006.

New Jersey Drinking Water Guidance for PFOA

Gloria B. Post, Ph.D., D.A.B.T
New Jersey Department of Environmental Protection

Presented at:
FSTRAC
Durham , NC
October 18, 2007

Background

- Preliminary guidance developed in response to request from water supply with PFOA detection.
- Finalized in February 2007.
- Starting point was EPA Draft Risk Assessment (2005) and Science Advisory Board comments (2006).

EPA Draft Risk Assesment

- Goal is to evaluate significance of general population's exposure to PFOA
- Half-life of PFOA much longer in animals than humans
- Comparison between animal studies and human exposures on basis of blood levels rather than external doses

EPA Draft Risk Assessment

(continued)

- Identified LOAELs and NOAELs for various non-cancer effects in animal studies.
- Evaluated cancer data and classified as "Suggestive" (EPA)/"Likely" (SAB)
- Developed Margins of Exposure between animal NOAELs/LOAELs and exposure of general population, based on comparison of blood levels.

EPA Draft Risk Assessment

(continued)

- Does not address external dose in humans (from water, food, soil, or air) which would result in a certain blood level.
- Does not develop Reference Dose or cancer slope factor.
- Relationship between external dose and blood level is needed to develop drinking water guidance.

External Dose vs. Blood Level

- Study of Ohio community with PFOA contamination of public water supply and private wells (Emmett et al., 2006).
- Observed approximately 100-fold concentration factor (1 ug/L in drinking water results in 100 ug/L in blood).
- Two independent modeling efforts give similar results.
- Mean blood level in general population is about 5 ppb.
- Approaches based on half-life should theoretically give same result.

Species	Endpoint	NOAEL or LOAEL	Animal Blood Level (ug/L)	UF	Target Human Blood Level (ug/L)	DW Conc. (ug/L)
Adult female rat	↓ Body Wt., Hematology	NOAEL 1.6 mg/kg/day (30 ppm)	1800	100	18	0.04
Adult male rat	↓ Body Wt, liver wt, and kidney weight	LOAEL 1 mg/kg/day	42,000	1000	42	0.08
Non-human primate	↑ liver wt. and possible mortality	LOAEL 3 mg/kg/day	77,000	3000	26	0.05
Pregnant female rat	↓ Pup Body Wt.	NOAEL 3 mg/kg/day	3500	100	35	0.07
Male rat pups	↓ Body Weight	NOAEL 3 mg/kg/day	9200	100	92	0.18
Female rat pups	↓ Body Weight	NOAEL 10 mg/kg/day	13,000	100	130	0.26
Male rats (cancer)	Leydig cell, pancreatic, and liver tumors	13.6 mg/kg/day (~10% tumor incidence)	572,000	NA*	5.7	0.06 (20% RSC not used)

*Linear extrapolation from 10^{-1} to 10^{-6} risk level.

Example of Calculation of Drinking Water Concentration

- LOAEL in adult male rat is **1 mg/kg/day** (↓ body wt., liver and kidney wt.) in two generation reproductive study.
- Blood concentration in rat at 1 mg/kg/day modeled at **42,000 ug/L**.
- UF of 1000 (chronic LOAEL) applied to blood level → **42 ug/L** target **human** blood concentration.
- 42 ug/L x 0.2 (RSC) = **8 ug/L** (Target contribution to blood concentration from drinking water exposure)
- Concentration factor between blood and drinking water is 100 → Target drinking water concentration is **0.08 ug/L**.

Drinking Water Guidance Value

- Similar calculation done for each non-cancer endpoint.
- Most sensitive endpoint is in adult female rat - 0.04 ug/L.
- For cancer, rat blood level at dose giving 10% tumor incidence extrapolated to 10^{-6} incidence - 0.06 ug/L. (No RSC used for cancer calculation).
- All endpoints gave similar values (0.04, 0.05, 0.06, 0.07, 0.08, 0.18, and 0.26 ug/L).
- Guidance value is 0.04 ug/L.

Uncertainties

- More recent studies show effects not considered.
- Some blood levels modeled, not measured.
- Half-life in female rat very short (hours) - steady state not reached with daily gavage and AUC used.
- Some data suggests male rat blood levels may be lower at dose of concern, so drinking water value based on this possibly too high.
- Larger study will give additional information on blood/drinking water concentration factor.

For Further Information

- Gloria.post@dep.state.nj.us
- http://www.nj.gov/dep/watersupply/pfoa_dwguidance.pdf

Q. Scott Stoner: Thank you. That was a very good presentation, and that is a chemical that we in New York are interested in as well. Could you just quickly go over the administrative process you went through for those values and what kind of public comment, if any, you got on it?

A. Gloria Post: It's a guidance value at this point, so the only administrative process that we went through was a lot of internal discussion between our group, the Safe Drinking Water Group, and the higher-level people at DEP. But it is not a regulation or a criterion or anything. It's on our agenda for possible future MCL development, but it is guidance for now.

Q. Mark Johnson: You used the relative source contribution for the noncancer endpoint and you did not use it for the cancer endpoint. What is the rationale for that? Is it a matter of policy?

A. Gloria Post: It is a matter of policy because, as I'm sure you know, for the noncancer risk assessments, for the reference dose, the theoretical basis is that there is a threshold. So you shouldn't exceed it and if you are below it, there shouldn't be an effect. But for cancer, if you are using a risk-level approach, any dose has some risks, so you can't say you have no risk. So, we say that the risk from exposure in water shouldn't be more than $1/10^6$. We don't say total exposure to the chemical in air and everything else shouldn't be more than $1/10^6$. It's not feasible. Does that answer your question?

Q. Mark Johnson: Not exactly, but that's okay.

C. Bruce Mintz: With the threshold, you don't want to exceed it. So with the cancer risk, theoretically you could do it, but there's no threshold. Basically, it is the cancer risk for that drinking water route. So, you could account for the other cancer risks, but it's not like with cancer you can say that we are going to try to keep cancer risks from all sources below a certain cancer risk level (e.g., $1/10^{-6}$).

C. Mark Johnson: It just seems as though the concept of applying it is that you have other sources of exposure and it doesn't seem to matter what the endpoint is, what the biological endpoint is.

C. Elizabeth Doyle: My understanding of the question [is] for anything that is cancer-based, you have a zero tolerance for any exposure. Because it is driving to zero, you try to reach that zero level. You don't partition it per source. If you are using a noncancer effect or a threshold for cancer, then you have a certain amount that is a tolerable exposure and that ends up being chopped up, if you will, or divided based upon food, industrial sources, air sources, and water, and whatever is left. The management issue is that they don't allow you to reach 100 percent of the RfD—or the goal is not to do that—so they try to crank down and have as much influence as possible on the water source. It is a combination of risk management and science.

C. Gloria Post: Maybe I didn't say this because I didn't go into this much background, but when EPA develops its MCLGs for carcinogens, its MCLG goal is zero. New Jersey's law and the way we do it is that for the MCLGs and drinking water guidance, we develop it ourselves as opposed to using the federal ones. Our law specifies a $1/10^6$ risk level from drinking water.

C. Elizabeth Doyle: For drinking water at the national level, there is a 10^{-4} to 10^{-6} range.

Calculation of a North Carolina Public Health Goal (Health-based Drinking Water Level) for Total Perfluorooctanoic acid (PFOA) and Perfluorooctane sulfonate (PFOS) Level

Luanne Williams
North Carolina Department of Health and Human Services
(919) 707-5912
Luanne.Williams@ncmail.net

Visuals follow. Please contact the speaker for more information.

Two Criteria Used

1. **<u>Systemic Threshold Concentration or Recommended Noncancer Health-based Concentration</u> - Chronic Oral Reference Dose mg/kg/day x 70 kg body weight x 0.20 (Relative Source Contribution or RSC) x 1 day/2L (Water Consumption Rate) = North Carolina Public Health Goal mg/L**

   The 5% lower limit benchmark dose ($LBMD_5$) (where 95% of the doses associated with a 5% response for early rat pup death is represented as the 95% confidence interval and the lower limit is the lowest dose of this interval) for the critical PFOS developmental effect (early rat pup death) is reported in the literature as 0.58 mg/kg/day (Lau C, Butenhoff JL, and Rogers JM, 2004. The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicology and Applied Pharmacology*. Volume 198. pp. 231-241). By interpolation of the data in Table 1 in this same paper, it is possible to estimate that a dose of 0.58 mg/kg/day of PFOS would produce a lower limit benchmark internal serum PFOS concentration associated with a 5% response ($LBMIC_5$) of approximately 20 ug/ml in the neonates in this study (2 mg/kg-day rat maternal administered dose/ 72 ug/ml rat newborn serum concentration = 0.58 mg/kg-day maternal rat administered dose/ X newborn serum concentration), which is similar to the PFOA 10% lower limit benchmark internal serum concentration ($LBMIC_{10}$) for early rat pup death of 29 ug/ml (Butenhoff JL et al. 2004, Characterization of risk for general population exposure to perfluorooctanoate*, Regulatory Toxicology and Pharmacology.* Volume 39. pages 363-380). The effects of both of these compounds in rats appear to be due in large part to their activation of PPAR-alpha (Peroxisome proliferator-activated receptor-alpha), a mode of action that is of questionable relevance to the human (US EPA January 4, 2005 Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and Salts; Butenhoff JL et al. 2004, Characterization of risk for general population exposure to perfluorooctanoate*, Regulatory Toxicology and Pharmacology.* Volume 39. pages 363-380).

   The rat developmental benchmark $LBMIC_5$ for PFOS of 20 ug/ml is also similar to the monkey liver $LBMIC_{10}$ for PFOA of 23 ug/ml (Lau C, Butenhoff JL, and Rogers JM, 2004. The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicology and Applied Pharmacology*. Volume 198. pp. 231-241; Butenhoff JL et al. 2004, Characterization of risk for general population exposure to perfluorooctanoate*, Regulatory Toxicology and Pharmacology.* Volume 39. pages 363-380). The monkey liver $LBMIC_{10}$ for PFOA of 23 ug/ml was used by Dr. Harvey Clewell with CIIT in the derivation of a recommended reference dose for PFOA of 0.00009 mg/kg-day (CIIT Centers for Health Research, Research Triangle Park, NC, Application of

Pharmacokinetic Modeling to Estimate PFOA Exposures Associated with Measured Blood Concentrations in Human Populations, Presentation of model and calculation of chronic oral reference dose made by Dr. Harvey Clewell to the NC Scientific Advisory Board on February 22, 2007 and soon to be published in approximately six months according to Dr. Clewell). These similarities provide some assurance that the use of the monkey $LBMIC_{10}$ for PFOA would provide a health-conservative basis for a provisional reference dose for PFOS. It is also assuring that the serum concentration associated with a no observed adverse effect level (NOAEL) for PFOS in the monkey is 83 ug/ml which is about four-fold higher than the monkey $LBMIC_{10}$ for PFOA of 23 ug/ml (Seacat AM et al., 2002. Subchronic Toxicity Studies on Perfluorooctanesulfonate Postassium Salt in Cynomolgus Monkeys. *Toxicological Sciences* Volume 68, pp. 249-264; Butenhoff JL et al. 2004, Characterization of risk for general population exposure to perfluorooctanoate*, Regulatory Toxicology and Pharmacology.* Volume 39. pages 363-380).

In general, it appears that the toxicities of PFOA and PFOS at the same blood concentrations are roughly similar, and that use of a benchmark concentration for PFOA in the monkey would be protective for the effects observed from PFOS. Moreover, the human half-lives of PFOA and PFOS are similar (4 and 5 years, respectively), and they appear to have similar distribution (extracellular) and metabolism (minimal) (personal communication Dr. Harvey Clewell, Director for Center for Human Health Assessment with CIIT at the Hamner Institutes Research Triangle Park, March 23, 2007; Apelberg BJ et al., 2007. Determinants of Fetal Exposure to Polyfluoroalkyl Compounds in Baltimore, Maryland. *Environ. Sci. Technol.*Volume 41, pp. 3891-3897; Olsen et al., 2005. Evaluation of the half-life ($T_{1/2}$) of elimination of perfluorooctanesulfonate (PFOS), perluorohexanesulfonate (PFHS) and perfluorooctanoate (PFOA) from human serum. Presented at FLUOROS: An international symposium on fluorinated alkyl organics in the environment August 19, 2005).

It is recommended to use the monkey $LBMIC_{10}$ for PFOA of 23 ug/ml and the CIIT pharmacokinetic modeling to derive a human chronic oral reference dose for PFOA and PFOS as presented by Dr. Harvey Clewell at the February 22, 2007 to the North Carolina Scientific Advisory Board. Since there is uncertainty about the relevance of using rodent effect data, using the monkey data will reduce uncertainty. Also, using the pharmacokinetic model will allow for a more realistic extrapolation from monkey to human equivalent levels as opposed to using higher default safety factors to account for the uncertainty in extrapolation from rodent to human levels.

According to the presentation made by Dr. Harvey Clewell, the lower bound 10% benchmark serum concentration response for monkeys based on liver weight is 23 ug/ml or 23,000 ng/ml (Butenhoff JL et al. 2004, Characterization of risk for general population exposure to perfluorooctanoate*, Regulatory Toxicology and Pharmacology.* Volume 39. pages 363-380). Using the pharmacokinetic model generated by CIIT, the equivalent human administered dose in ng/kg-day can be roughly estimated as 0.12 times the plasma concentration in ng/ml (ng/kg-day equivalent human administered dose = 0.12 x ng/ml serum level in monkeys). The monkey lower bound benchmark serum concentration was reported as 23,000 ng/ml. Using the CIIT data, 0.12 times the 23,000 ng/ml would correlate to an equivalent human administered dose of 2,760 ng/kg-day. Dr. Clewell with CIIT recommended a safety factor of 30 be applied to the equivalent human administered dose of 2,760 ng/kg-day (3 animal to human and 10 for human variability) to derive the human equivalent administered dose of 90 ng/kg-day or 0.00009 mg/kg-day. An

additional safety factor of 10 was not applied to take into account the use of a subchronic study because monkeys reached steady state within the six month study, so observed serum levels would reflect serum levels beyond six months or chronic exposure. Therefore, the blood serum levels within the six month study period would be representative of serum levels from chronic exposure. Because steady state was reached, then effects reported for the six month period would be expected to be somewhat similar to effects for chronic exposure. A systemic threshold concentration can be calculated as shown using the calculated chronic oral reference dose of 0.00009 mg/kg-day:

0.00009 mg/kg/day x 70 kg x 0.20 (RSC) x 1 day/2L = 0.00063 mg/L

Note: The chronic oral RfD of 0.00009 mg/kg/day is based on a subchronic monkey study where the critical effect reported was increased liver weight.

RSC = Relative Source Contribution

2. **<u>One in a Million Excess Cancer Risk</u>**

PFOA is carcinogenic in rodents by multiple mechanisms and in multiple organ systems. Based on no adequate human studies and uncertain relevance of the tumors from rat studies for PFOA, there is suggestive evidence of carcinogenicity according to EPA. Epidemiological studies on the effects of PFOA in humans have been conducted on workers. A retrospective cohort mortality study demonstrated a statistically significant association between prostate cancer mortality and employment duration in the chemical facility of a plant that manufactures PFOA. However, in an update to this study in which more specific exposure measures were used, a significant association for prostate cancer was not observed. Other mortality studies lacked adequate exposure data which could be linked to health outcomes. Cholesterol and triglyceride levels in workers were positively associated with PFOA exposures, which is inconsistent with the hypolipidemic effects observed in rat studies. A statistically significant positive association was reported for PFOA and T3 thyroid hormone levels in workers but not for any other thyroid hormones. Due to lack of data, a one in a million excess cancer risk level cannot be calculated at this time (US EPA 2005b. Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and Its Salts. US Environmental Protection Agency Office of Pollution Prevention and Toxics Risk Assessment Division, January 4, 2005. http://www.epa.gov/opptintr/pfoa/pubs/pfoaex.pdf; 2006 USEPA. Memorandum from Christopher Weis, Senior Toxicologist with US EPA Office of Criminal Enforcement, Forensics and Training to Walker Smith, Office of Civil Enforcement, November 17, 2006).

The recommended NC Public Health Goal for PFOA and PFOS is 0.00063 mg/L or 0.63 ug/L. According to the literature, a PFOA blood serum level is equal to 100 times that of the drinking water level. Drinking water at 0.63 ug/L may correspond to a blood serum level of 63 ug/L or 63 ng/mL. The median serum PFOA level for the general population is 4 to 5 ng/mL and occasionally values may go above 20 ng/mL (Emmett EA et al., 2006. Community Exposure to Perfluorooctanoate: Relationships between Serum Concentrations and Exposure Sources. *JOEM*, Volume 48, Number 8, August 2006).

Development of NCPHG for Total PFOA and PFOS

Luanne K. Williams, Pharm.D.,
Toxicologist
North Carolina Department of
Health and Human Services
Occupational and Environmental
Epidemiology Branch

PFOA and PFOS Similar in Toxicity and Kinetics

- LBMIC early rat pup death
  - $LBMIC_5$ PFOS 20 ug/mL (Lao C et al., 2004)
  - $LBMIC_{10}$ PFOA 29 ug/mL (Butenhoff JL et al., 2004)
- Effects in rats in large part due to activation of Peroxisome proliferator-activated receptor-alpha (PPAR-alpha)
- Half-lives PFOA and PFOS of 4 and 5 years

Rat Developmental Benchmark for PFOA and PFOS Similar to Monkey Liver Benchmark for PFOA and PFOS

- LBMIC early rat pup death
  - $LBMIC_5$ PFOS 20 ug/mL (Lao C et al., 2004)
  - $LBMIC_{10}$ PFOA 29 ug/mL (Butenhoff JL et al., 2004)
- $LBMIC_{10}$ monkey increased liver weight for PFOA 23 ug/mL (Butenhoff JL et al., 2004)
- NOAEL for liver effects in monkeys for PFOS at 83 ug/mL (Seacat et al., 2002)

Monkey Liver $LBMIC_{10}$ and Pharmacokinetic Model → Reference Dose

- **Primate instead of rodent serum concentrations were used because of possible PPAR-alpha mechanism in rodents**
- **PFOA and PFOS similar in toxicity with similar effects**
- **Used CIIT pharmacokinetic model to allow for more realistic extrapolation from monkey to human serum levels**
- **Reduced uncertainty and use of higher default safety factors**

Pharmacokinetic Model Presented to NCSAB by Dr. Harvey Clewell with CIIT at RTP, NC

- Dr. Clewell is Director for Center for Human Health Assessment at CIIT
- Physiologically motivated description of PFOA kinetics in monkey was scaled to human kinetics
- Human PFOA Model Parameters
  - Body weight, cardiac output, volume of renal filtrate, renal filtration rate, volume of distribution, transport maximum, transport affinity, transfer rate constants, free fraction in plasma
  - Validated against data from Little Hocking, Ohio population who were exposed to high concentrations of PFOA in drinking water

Calculation of Chronic Oral Reference Dose for PFOA and PFOS

- $LBMIC_{10}$ monkey increased liver weight for PFOA 23 ug/mL or 23,000 ng/mL
- Using PK model by CIIT, equivalent human administered dose in ng/kg-day is 0.12 times the monkey plasma concentration in ng/mL

  23,000 ng/mL x 0.12 = 2,760 ng/kg-day
- Dr. Clewell with CIIT recommended a safety factor of 30 (3 animal to human and 10 for human variability)

  2,760 ng/kg-day / 30 safety factor = 90 ng/kg-day or 0.00009 mg/kg-day

Calculation of NCPHG for Total PFOA and PFOS

0.00009 mg/kg-day x 70 kg x 0.20 (RSC) x 1 day/2L = 0.00063 mg/L or 0.63 ug/L

Q. Gloria Post: The primate study you used, I assume, is the same one identified by USEPA. It's a 6-month study, and why wasn't a factor for subchronic-to-chronic included? I could see using 3 for animal-to-human for primates instead of 10, but 6 months is subchronic for a primate.

A. Luanne Williams: Dr. Clewell is relying on the parameters presented in the last few slides for the model.

Q. Gloria Post: Then it doesn't have anything to do with the subchronic-to-chronic for the toxicity endpoint?

A. Luanne Williams: Dr. Clewell was looking at the predicted serum levels over time. He looked at Little Hocking, Ohio, data. He looked at their serum levels over several years.

Q. Gloria Post: This is only if the animals were exposed for a subchronic period. If they were exposed longer, would effects have occurred at lower doses or more dramatic effects?

A. Luanne Williams: But the modeling parameters do take into account long-term exposure.

C. Mark Johnson: But you probably reach steady-state conditions in serum levels by 6 months, so extending it beyond that is unlikely to elevate it. If your dose-response is related to serum levels, this exposure period is relevant.

C. Helen Goeden: We can only speculate on why Dr. Clewell didn't apply it, but I can tell you why we didn't apply it. Whether his is the same rationale, I don't know. It's true that we don't have anything longer than 6 months in monkeys, but we looked at other species, particularly the rat, and it looked as though regardless of the length of exposure the thing that was consistent was the serum level that was achieved and of concern. Based on that information, we did not apply an additional chronic uncertainty factor, based on the fact that if they had achieved a certain serum level, it didn't appear that longer exposure resulted in any lower effect level. I think that additional studies that have been done since then have only reinforced that.

C. Luanne Williams: Also, the steady state for the monkeys would have been reached a lot sooner and certainly would have been reached within a 6-month time period. The 6-month study represents more of a long-term exposure period for the monkeys because they would have reached steady state, and that would be applicable.

C. Gloria Post: I'm sorry. I don't want to start an argument, but I'm not talking about serum levels. It's just that how do you know if they were exposed whether the serum levels stayed the same or went down? How do you know that effects wouldn't have been seen at lower doses if they were exposed for their whole life? It's not a matter of their serum levels. Just like mice had certain serum levels but they got effects when they got older that you perhaps wouldn't have seen in a subchronic period.

C. Helen Goeden: I think it is because of the developmental, even though it is a short period of time. And then in other studies, whether it is 2 weeks, 28 days, 90 days, or 2 years, what's been consistent across that with PFOA is the serum level, which elicits the effects at the low levels regardless of how long they have been exposed.

Perfluorochemicals in Minnesota – Derivation of Health Protective Criteria

Helen Goeden
Minnesota Department of Health
(651) 201-4904
helen.goeden@health.state.mn.us

Visuals follow. Please contact the speaker for more information.

In late 2004 the Minnesota Department of Health (MDH) began sampling public and private water supplies to investigate possible impacts from past perfluorochemicals (PFC) waste disposal. The MDH expanded the number of PFCs analytes from two (PFOS and PFOA) to seven (PFBS, PFHxS, PFBA, PFPeA, PFHxA). All analytes have been detected in groundwater.

Over the last year the MDH and Minnesota Pollution Control Agency (MPCA) have derived or revised health based criteria for PFOS and PFOA for groundwater, fish tissue, surface water and soil. A health based criteria for PFBA for groundwater is currently under development.

The presentation will provide a brief overview of the extent of the contamination, the basis of the media specific criteria and on-going PFC related activities in Minnesota.

Perfluorochemicals in Minnesota - Derivation of Health Protective Criteria

FSTRAC

October 18, 2007

Helen Goeden, Ph.D.
Minnesota Department of Health

Contributors:
James Kelly, Virginia Yingling, & Pat McCann (MDH) and Dann White and Emily Hansen (MPCA)

Outline

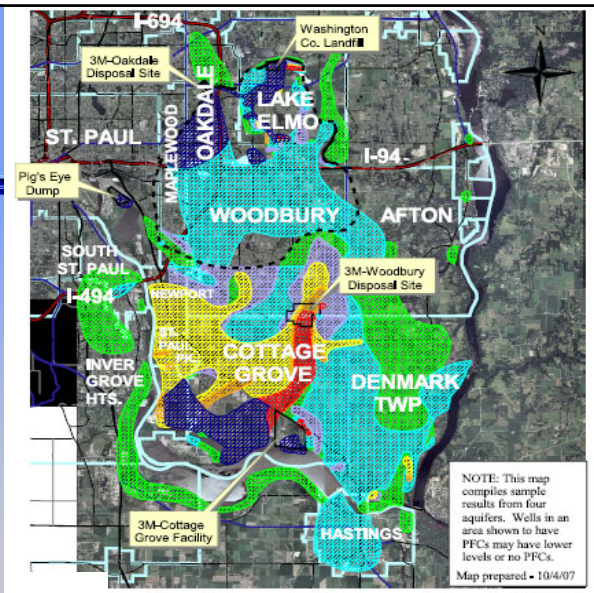
- Background
- Minnesota Health-based Criteria
  - Groundwater/Drinking Water
  - Fish Advisories
  - Surface Water
  - Soil Screening Values
- Ongoing Activities in Minnesota
- Guidelines from Other Agencies

Background

- 2006 MDH expanded list of PFC analytes beyond PFOA and PFOS to include:
  - PFBA (perfluorobutanoic acid)
  - PFPeA (perfluoropentanoic acid)
  - PFHxA (perfluorohexanoic acid)
  - PFBS (perfluorobutane sulfonate)
  - PFHxS (perflurohexane sulfonate)

Background –

Media	Maximum Detected Concentration (ppb)		
	PFBA	PFOA	PFOS
Groundwater	1,170	23,700	8,343
Drinking water	11.8	3.2	3.4
Surface Water	1.08	20.4	11
Fish	ND	20.1	5150
Soil	1,600	18,050	108,000



Health Guidelines – PFOA Health Risk Limit

- Critical Study Point of Departure
  - 3 mg/kg-day LOAEL, based on increase liver weight in monkeys
- Human Equivalent Calculation
  - 0.043 mg/kg-day (half-life adjusted, 3/70)
- Application of Uncertainty Factors
  - 3 interspecies toxicodynamics; 10 intraspecies variability, and 10 LOAEL-to-NOAEL
- Reference Dose – 0.00014 mg/kg-day

Reference Dose based on bench-mark serum concentration as point of departure = 0.00008 mg/kg-day

Health Guidelines – PFOA Health Risk Limit (cont)

$$0.5 \text{ ug/L} = \frac{\text{RfD (mg/kg-d) x RSC x 1,000}}{\text{Intake Rate (L/kg-day)}}$$

Where:

RfD – 0.00014 mg/kg-day

RSC – 0.2

Intake Rate – 0.053 L/kg-day

http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/pfoamemo0307.pdf

Health Guidelines – PFOS Health Risk Limit

- Critical Study Point of Departure
  - 0.15 mg/kg-day LOAEL, based on decreased HDL and T3 levels (NOAEL 0.03 mg/kg-day)
- Human Equivalent Calculation
  - 0.0075 mg/kg-day (half-life adjusted, 0.15/20)
- Application of Uncertainty Factors
  - 3 interspecies toxicodynamics; 10 intraspecies variability, and 3 LOAEL-to-NOAEL
- Reference Dose – 0.000075 mg/kg-day

Health Guidelines – PFOS Health Risk Limit (cont)

$$0.3 \text{ ug/L} = \frac{\text{RfD (mg/kg-d) x RSC x 1,000}}{\text{Intake Rate (L/kg-day)}}$$

Where:

RfD – 0.000075 mg/kg-day

RSC – 0.2

Intake Rate – 0.048 L/kg-day

http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/pfosmemo0307.pdf

Health Guidelines – Groundwater used as drinking water (cont)

- PFBA - - have used advisory value of 1 ug/L, however, Health Based Value is under development
- PFPeA and PFHxA – have used 1 ug/L as advisory value
- PFBS and PFHxS – have used 0.6 ug/L as advisory value
- Look at all PFCs together (additivity)

Current practice – may change as additional information becomes available.

Health Guidelines –
MDH Fish Consumption Advice

PFOS -

- Reference Dose - 0.000075 mg/kg-day
- Meal Ratio - 227 g fish/70 kg body weight (same ratio for other body weights)
- Limit meals based on concentration in fish
  - > 38 ppb = 1 meal per week
  - > 160 ppb = 1 meal per month

http://www.health.state.mn.us/divs/eh/fish/eating/testedwaterspfcs.html

Health Guidelines –
Surface water

Drinking Water + Fish Consumption

$$= \frac{\text{RfD (mg/kg-d) x 70 kg x K}}{\text{2 L/kg + [0.03 kg/d x BAF]}}$$

Mississippi River (Pool 3): 0.006 ug/L (PFOS) and 0.72 ug/L (PFOA)

Lake Calhoun: 0.0122 ug/L (PFOS) and 0.61 ug/L (PFOA)

http://www.pca.state.mn.us/publications/pfoa-report.pdf
http://www.pca.state.mn.us/publications/pfos-report.pdf

Health Guidelines – Surface water (cont)

Fish Consumption

$$= \frac{\text{RfD (mg/kg-d) x 70 kg x K}}{\text{0.01L/kg + [0.03 kg/d x BAF]}}$$

Mississippi River (Pool 3): 0.0061 ug/L (PFOS) and 2.7 ug/L (PFOA)

Lake Calhoun: 0.01248 ug/L (PFOS) and 1.62 ug/L (PFOA)

Health Guidelines – Soil Screening Values

- Residential Land Use
  - PFOA 4 mg/kg
  - PFOS 2 mg/kg
- Industrial Land Use
  - PFOA 23 mg/kg
  - PFOS 12 mg/kg

http://www.pca.state.mn.us/publications/risk-tier2srv.xls

Ongoing Activities – Minnesota

- Derivation of less-than-chronic HRLs for PFOA and PFOS for promulgation later this year
- Use of serum levels as POD for PFOA (&PFOS)?
- Potential impact of high intake rates during early-life on serum levels?
- Derivation of HBV for PFBA
- Laboratory development of analytical methods for additional PFCs, lower detection limits
- Ongoing site monitoring and investigations (including fish & ambient investigation)
- Treatability studies for managing discharge from disposal sites
- Point of use treatment study for households

PFC Information Web Sites

Minnesota Department of Health (MDH)

http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/index.html

- Pefluorochemicals and Health
  - Information sheets
  - HRL and HBV
  - Fish Advisories
- Community Information
  - Information sheets and maps for contaminated areas
- May 2007 Workshop: PFCs and Health in Minnesota

PFC Information Web Sites

Minnesota Pollution Control Agency (MPCA)
http://www.pca.state.mn.us/hot/pfc.html

- Latest News
- Fact Sheets and presentations
- Water Quality Criteria for PFOA and PFOS
- Sampling and pilot test for groundwater treatment
- Sediment and fish tissue sampling
- Wastewater survey
- Testing at landfills

Guidelines by Other Agencies

- EPA SDWA 1431 Consent Order – DuPont Washington Works facility (Nov 2006)
  - PFOA 0.50 ug/L
    www.epa.gov/region03/enforcement/dupont_order.pdf
- German Drinking Water Commission (July 2006)
  http://www.uba.de/uba-info-presse-e/hintergrund/pft-in-drinking-water.pdf
  - PFOA and PFOS combined:
    - Action Level 5 ug/L
    - Provisional value for infants 0.5 ug/L
    - Lifetime Value ≤ 0.3 ug/L
    - Goal ≤ 0.1 ug/L

Guidelines by Other Agencies (cont)

- UK Governmental Committee on Toxicity (COT) Statement on the TDI (July 2006)
  - PFOA - 3 ug/kg-d (http://www.food.gov.uk/multimedia/pdfs/cotstatementpfoa200610.pdf)
  - PFOS – 0.3 ug/kg-d (http://www.food.gov.uk/multimedia/pdfs/cotfinalminutes11jul2006.pdf)
- UK Drinking Water Inspectorate (May 2007)
  http://www.dwi.gov.uk/regs/infolett/2007/info0507.pdf
  - Tier 1 (monitor) - > 0.3 ug/L (PFOS or PFOA)
  - Tier 2 (take action to reduce levels as soon as practicable) - > 1.0 (PFOS) & > 10.0 (PFOA)
  - Tier 3 (take action to reduce levels as soon as possible) - > 10.0 (PFOS) & > 90.0 (PFOA)

Questions, Answers, and Comments

Q. Mark Johnson: I had a question about the fish sampling. Is there any indication that there are differences in species that suggest that bottom feeders may have different levels than other species?

A. Helen Goeden: There are differences in species. It certainly doesn't follow your typical pattern for PCBs or mercury where your predator fish have the highest concentrations. My understanding, too, is that sometimes the smaller fish have the higher concentrations, so it is a mystery. There are some investigations looking at sediments, water, and insects—trying to look at where these fish may be picking this up.

Q. Mark Johnson: Are there any indications that sediment is a significant reservoir?

A. Helen Goeden: Not that I know of. That is actually being debated. Some people feel that these chemicals are actually right at the surface of the water. Since they are surfactants, they form this thin layer, and insects that are at that layer and fish that feed on those insects are more highly exposed. But at this point I think it is sort of speculation. Those are things that people are looking into.

C. Ambika Bathija: We haven't taken a break. Feel free to stretch your legs. Bill Russo is going to chair our next session.

Cardiac, Diabetic and Cancer-related Risks from Chronic Arsenic Exposure in Inner Mongolia

Judy Mumford
U.S. Environmental Protection Agency
(919) 966-0651
mumford.judy@epa.gov

Please contact the speaker for more information.

Chronic arsenic exposure via drinking water has been associated with human cancers, diabetes and cardiovascular diseases and has been of great public health concern world wide. The objectives of this study were to investigate health effects of arsenic, including mode of action, and to assess dose-response relationships of arsenic on cardiovascular, diabetic and cancer-related effects in Ba Men, Inner Mongolia. Ba Men residents (a total of 654 study subjects) chronically exposed to 0.1 to 826 μg/L of arsenic concentrations via drinking water participated in this study. Arsenic exposure was assessed by determining arsenic levels in well water, nail and urine. Arsenic effects examined included:(1) ECG QT interval prolongation for cardiovascular effects, (2) hemoglobin A1c (glycosylated hemoglobin) for diabetes risk, and (3) DNA fragmentation and chromosome damage, gene expression of DNA repair genes (*OGG1* and *ERCC1*) and human telomerase reverse transcriptase (hTERT) which is relevant in cell proliferation. ECG QTc intervals were determined. QTc interval ≥ 0.45 seconds was considered to be prolonged. The results showed that QTc interval prolongation was associated with water arsenic levels ($p<0.001$) showing a dose-response relationship. Females were more susceptible to QT interval prolongation than males. Hemglobin A1c was determined in blood samples and showed positive association with water arsenic levels ($p<0.001$). DNA fragmentation in buccal cells tested by TUNEL assay was associated arsenic exposure starting at high levels of arsenic exposure (430-690 μg/L), whereas increased micronucleus frequency (a measurement for chromosome damage) was associated with arsenic exposure starting at lower concentrations (100-300 μg/L). The mRNA levels for *OGG1*, *ERCC1* and *hTERT* in blood cells were positively associated with water arsenic levels ($p<0.01$). These results demonstrated that we were able to use the ECGs and biomarkers to link arsenic exposure to cardiac effects, diabetic risk and cancer-related effects showing dose-response relationships. (This abstract does not reflect EPA policy.)

Questions, Answers, and Comments

Q. Ken Rudo: There seems to be a gap somewhat between 21 ppb and 100 ppb. Looking at the data, would you say that you would see some noncancer effects in that range? Some of the information you had up there seems to indicate that you would.

A. Judy Mumford: Yes, we will. Our first study was a range-finding study. Our second study is a low-dose study. We have more than 600 study subjects from which we are collecting EKG data. We are going to have some low-dose data available. We are now analyzing the EKG data. That is a very good question. I do believe that cardiovascular effects will be a very sensitive marker of effects that can help us to look at low-dose health effects. I think even more so, maybe, than the cancer. That is why we now are emphasizing it more. We are still going to study cancer effects, but now we're looking at the cardiovascular studies.

Q. Luanne Williams: Does your slide say less than 21 ppb?

A. Judy Mumford: Yes, it says less than 21 ppb. Now we are going to have exposures from below detection all the way to 800 ppb. But 70 percent of our population are subjects exposed to 0 to 200 ppb, so we'll have a lot of emphasis on lower-level exposures. Now we can go back to the EKG data. EKG is kind of cheap compared with the biomarker, so we measured it in all 700 subjects. And we have nail data. It is well characterized. So all these 700 EKG individuals will have good exposure data to link to this.

Arsenic-Susceptibility & In Utero Effects

David Thomas
U.S. Environmental Protection Agency, National Health and
Environmental Effects Research Laboratory
(919) 541-4974
thomas.david@epa.gov

Visuals follow. Please contact the speaker for more information.

Exposure to inorganic arsenic remains a serious public health problem at many locations worldwide. If has often been noted that prevalences of signs and symptoms of chronic arsenic poisoning differ among various populations. For example, skin lesions or peripheral vascular disease are not uniformly observed in all exposed populations. Among members of a single population exposed to inorganic arsenic, some individuals manifest signs and symptoms of toxicity while other individuals with similar levels of exposure remain disease free. This intra- and inter-population variability in response may be explained in part by differences in susceptibility to the adverse effects of arsenic. The determinants of susceptibility are often divided into intrinsic factors such as genetics or life stage and extrinsic factors such as pre-existing disease or nutritional status. In this presentation, the role of genetics and life stage will be considered as susceptibility factors that determine response to exposure to inorganic arsenic. Recent results confirm that genetic polymorphisms in arsenic (+ 3 oxidation state) methyltransferase, the enzyme that catalyzes the methylation of arsenic, affect the pattern of arsenic metabolites present in urine. Other evidence suggests that exposure to inorganic arsenic in early life may predispose individuals to occurrence of cardiovascular disease and cancer and may adversely affect neurodevelopment. Additional research is needed to evaluate the role of these susceptibility factors as potentiators of the effects of chronic exposure to inorganic arsenic. Incorporating this information into risk assessments may better protect the public health. (This abstract does not reflect US EPA policy.)

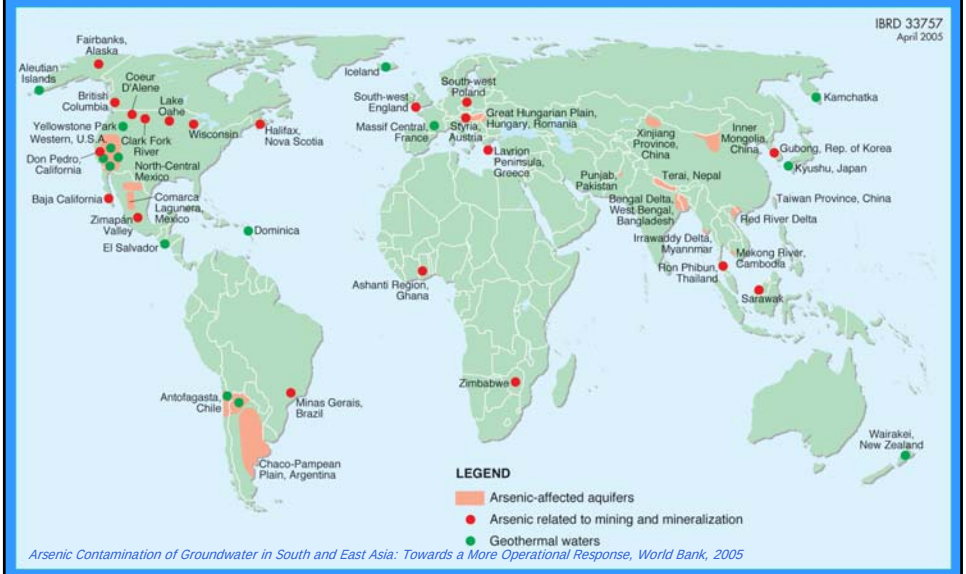
Arsenic - Susceptibility & In Utero Effects

David J. Thomas
PKB, ETD, NHEERL, ORD
U.S. Environmental Protection Agency

Federal-State Toxicology and Risk Analysis Committee Meeting
Durham, NC
October 18, 2007

- Arsenic as a public health issue
- Susceptibility – Intrinsic and extrinsic factors
- Genetic determinants of capacity for arsenic metabolism and disease susceptibility
- Sensitivities of developing organisms to arsenic
  - Animal models
  - Human data
- Research needs and future directions

Human exposures to inorganic arsenic occur worldwide



Arsenic Contamination of Groundwater in South and East Asia: Towards a More Operational Response, World Bank, 2005

Cancers associated with chronic occupational or environmental exposures to inorganic As

- **Skin**
- **Lung**
- **Liver**
- **Urinary Bladder**
- **Kidney**
- **Bone**

Other adverse health effects of chronic inorganic As exposure

- **Peripheral Vascular Disease**
- **Cardiovascular Disease**
- **Cerebrovascular Disease**
- **Type 2 Diabetes**
- **Peripheral Neuropathy**
- **Central Nervous System Dysfunction / Altered Neurodevelopment**
- **Adverse Effects on Reproductive Outcome**

Humans convert inorganic arsenic to methylated metabolites

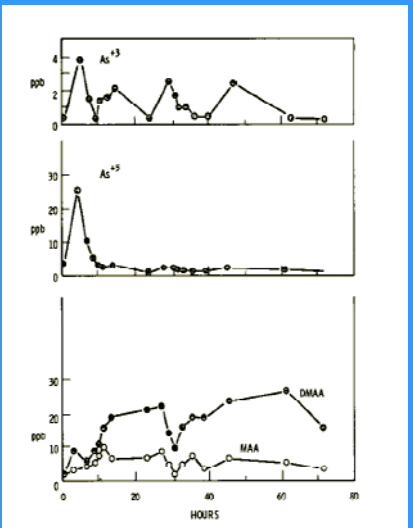


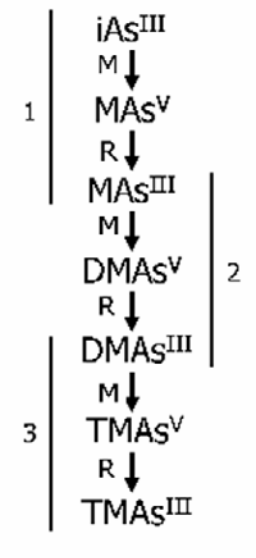
FIGURE 3. Concentration of arsenic compounds in urine with time after ingestion of well-water containing 200μg As^{+5}. The concentration of MAA and DMAA are given in ppb as arsenic.

Crecelius 1977

Ingestion of water containing 200 μg As^{V} leads to excretion of As^{V}, As^{III}, methyl As and dimethyl As in urine.

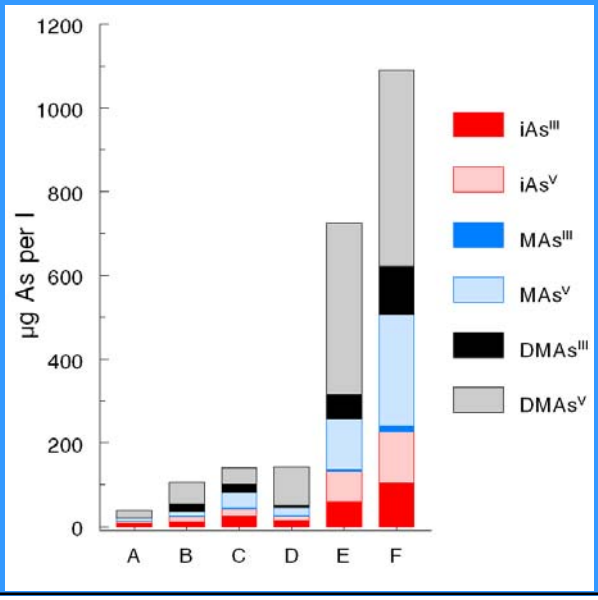
Inorganic As → Methyl As → Dimethyl As

Chemical pathway for arsenic methylation – Challenger's scheme



- **In the Challenger scheme, the overall pathway consists of two types of linked reactions. In the first, a trivalent arsenical undergoes oxidative methylation (M), yielding a methylated product containing pentavalent arsenic. This product is the substrate for a reductive reaction (R) that converts pentavalent arsenic to trivalency. At least three methyl groups can be added to an arsenic atom in an alternating series of these reactions.**

Urinary arsenicals contain both trivalent and pentavalent arsenic



There is only one arsenic methyltransferase and Arsenic (+3 oxidation state) Methyltransferase is its name

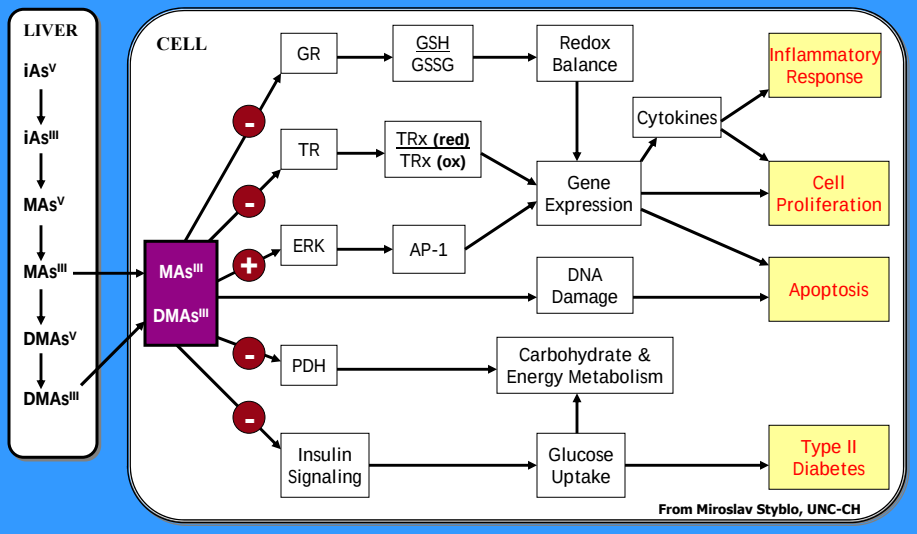
The *AS3MT* gene encodes a protein

- That is necessary and sufficient to catalyze all steps in the methylation pathway
- Altered expression of this protein (heterologous expression and gene silencing) produces changes in the arsenic methylation phenotype

This means

- no need to invoke other proteins as components of the methylation pathway
- if other proteins contribute, their contribution is not necessarily critical

Toxic effects of methylated trivalent arsenicals



Methylation is Activation.

Susceptibility

"Some individuals are more susceptible to environmental exposures due to **intrinsic** factors such as *life stage* or *genetics* and **acquired** factors such as *preexisting disease* or *nutrition*."

Genetic determinants of capacity for arsenic metabolism and disease susceptibility

```
                                    32                                61      72        85
H. sapiens      MAALRDA-EIQKDVQTYYGQVLKRSADLQTNGCVTTARPVPKHIREALQNVHEEVALRYYGCGLVIPEHLENCWILDLGSGSGRDCYVLSQLVGEKGHVTGIDMTKGQVE 109
R. norvegicus   MAAPRDA-EIHKDVQNYYGNVLKTSADLQTNACVTPAKGVPEYIRKSLQNVHEEVISRYYGCGLVVPEHLENCRILDLGSGSGRDCYVLSQLVGQKGHITGIDMTKVQVE 109
M. musculus     MAASRDADEIHKDVQNYYGNVLKTSADLQTNACVTRAKPVPSYIRESLQNVHEDVSSRYYGCGLTVPERLENCRILDLGSGSGRDCYVLSQLVGEKGHVTGIDMTKVQVE 110

                                                  156                                                   206
H. sapiens      VAEKYLDYHMEKYGFQASNVTFIHGYIEKLGEAGIKNESHDIVVSNCVINLVPDKQQVLQEAYRVLKHGGELYFSDVYTSLELPEEIRTHKVLWGECLGGALYWKELAVL 219
R. norvegicus   VAKAYLEYHTEKFGFQTPNVTFLHGQIEMLAEAGIQKESYDIVISNCVINLVPDKQKVLREVYQVLKYGGELYFSDVYASLEVSEDIKSHKVLWGECLGGALYWKDLAVI 219
M. musculus     VAKTYLEHHMEKFGFQAPNVTFLHGRIEKLAEAGIQSESYDIVISNCVINLVPDKQQVLQEVYRVLKHGGELYFSDVYASLEVPEDIKSHKVLWGECLGGALYWKDLAII 220

                      226                 250                 271
H. sapiens      AQKIGFCPPRLVTANLITIQNKELERVIGDCRFVSATFRLFKHSKTGPTKRCQVIYNGGITGHEKELMFDANFTFKEGEIVEVDEETAAILKNSRFAQDFLIRPIGEKL 329
R. norvegicus   AKKIGFCPPRLVTANIITVGNKELERVLGDCRFVSATFRLFKLPKTEPAGRCQVVYNGGIMGHEKELIFDANFTFKEGEAVEVDEETAAILRNSRFAHDFLFTPVEASL 329
M. musculus     AQKIGFCPPRLVTADIITVENKELEGVLGDCRFVSATFRLFKLPKTEPAERCRVVYNGGIKGHEKELIFDANFTFKEGEAVAVDEETAAVLKNSRFAPDFLFTPVDASL 330

                      334                 360   368/369 375
H. sapiens      PTSGGCSALELKDIITDPFKLAEESDSMKSRCVPDAAGGCCGTKKSC 375
R. norvegicus   LAPQ------TKVIIRDPFKLAEESDKMKPRCAPEGTGGCCGKRKSC 369
M. musculus     PAPQGRSELETKVLIRDPFKLAEDSDKMKPRHAPEGTGGCCGKRKNC 376
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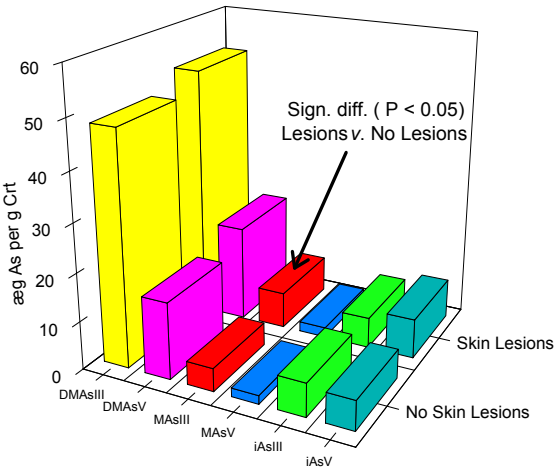
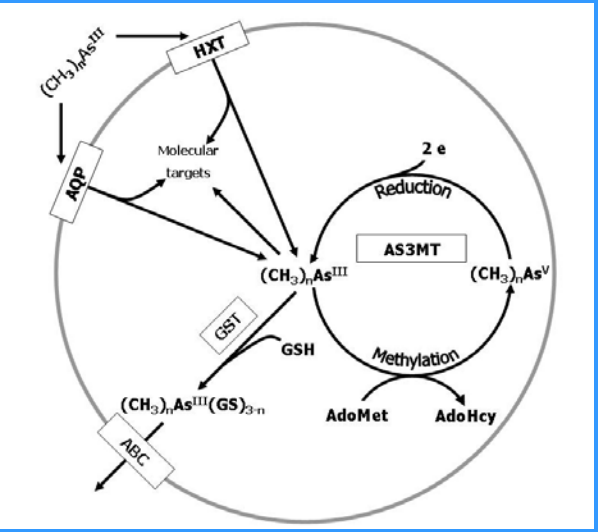
Methyl As III in urine and skin lesions



Valenzuela OL, Borja-Aburto VH, Garcia-Vargas GG, Cruz-Gonzalez MB, Garcia-Montalvo EA, Calderon-Aranda ES, Del Razo LM. Environ Health Perspect. (2005) 113:250-254.

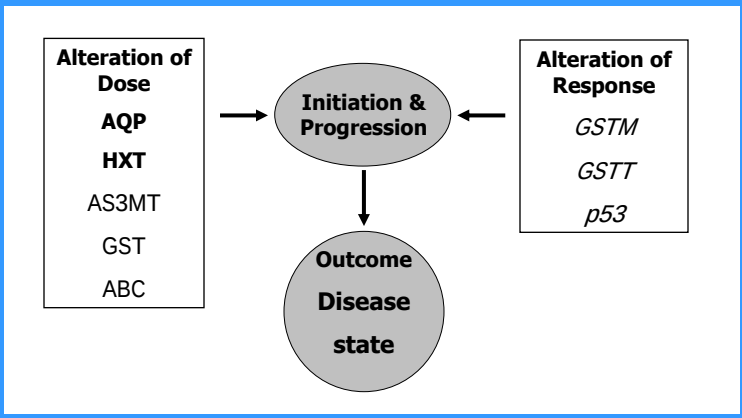
Individuals with skin lesions excrete a higher concentration of MAs(III) in urine than do individuals without skin lesions

A conceptual model for cellular arsenic metabolism



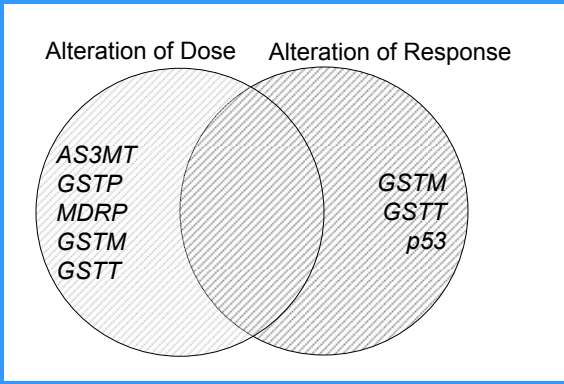
Variability in the function of any of the molecules involved in cellular metabolism can affect uptake, metabolism, and retention of arsenicals. This can change the dose of the critical arsenical species at the site of action.

Multiple factors can interact to determine outcome



Example – Urinary bladder cancer in humans chronically exposed to inorganic arsenic

Some susceptibility factors may be influencing multiple processes



Genotypic variation can change metabolic profiles

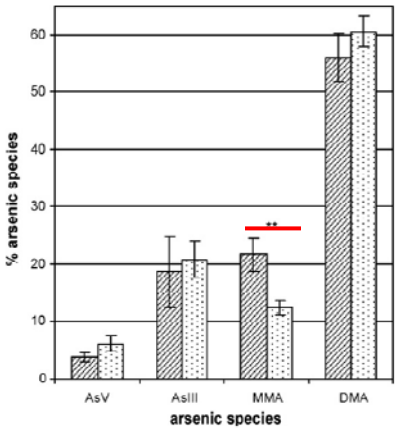


Fig. 3. Variation in the arsenic excretion profile in carriers of the G/C (promoter-114) and $Met_{287}Thr$ (exon 9) polymorphisms. ▨ : promoter-114/exon 9 variant carriers; $N = 13$; ⬚ : promoter-114/exon 9 wild carriers; $N = 37$. $^{**}t$-test, $P = 0.002$.

Hernandez et al., in press, 2007

Two common polymorphisms in the AS3MT gene are associated with an increased percentage of methyl arsenic in urine.

Is altered disease susceptibility associated with this change in metabolic profile?

Connecting genotypes and phenotypes

Genotypic Variation
(SNP)

↓

Altered Enzyme Function

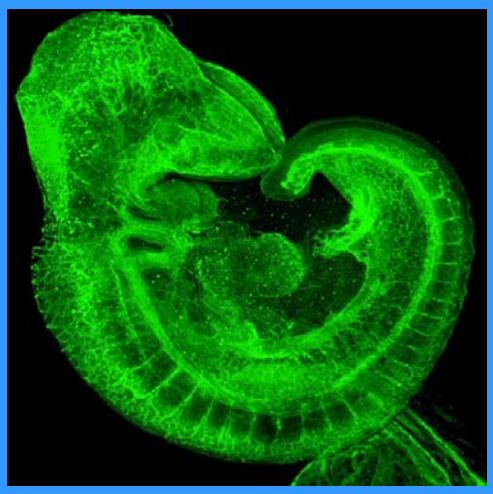
↓

Phenotypic Variation in Metabolic Profile
(more MAs, less DMAs)

↓

Phenotypic Variation in Disease Susceptibility

Sensitivities of developing organisms to arsenic

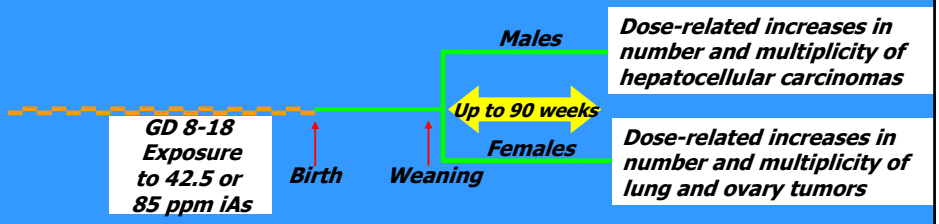


Special features of fetal development

- Fetus wholly dependent on maternal system for provision of nutrients (and exposure to toxins)
- Period of rapid growth and differentiation
- Critical periods in development when processes of growth and maturation must occur
  - cell proliferation in developing organs
  - cell migration
  - development of specialized function
  - disruptions can cause irreversible changes which may lead to disease later in life

Inorganic arsenic is a transplacental carcinogen in mice

Timing of exposure affects carcinogenic actions



Work of Michael Waalkes and associates at NCI

Perinatal exposure to inorganic arsenic

Transplacental exposure – In maternal-newborn pairs examine concentrations of inorganic arsenic and its metabolites. Find strong association between total arsenic in maternal and cord blood and between the concentrations of inorganic, methyl, and dimethyl arsenic in maternal and cord blood. Level of homocysteine in maternal blood strongly predicts fraction of dimethyl arsenic in cord blood.

Comment – Evidence that human fetus is exposed to inorganic arsenic and its methylated metabolites.

Reference – Hall, M. , et al., 2007, Determinants of arsenic metabolism: Blood arsenic metabolites, plasma folate, cobalamin and homocysteine concentrations in maternal-newborn pairs. Environmental Health Perspectives, 115:15037.

Perinatal exposure to inorganic arsenic

Moringa incident – In 1955, ~ 12000 infants in Japan were exposed to inorganic arsenic as a contaminant of milk powder. At least 100 infants died. Common early symptoms and signs included fever, diarrhea, and skin pigmentation. Among survivors, find increased prevalences of mental retardation and neurological disorders.

Limitations – Difficult to estimate exposures, lack of uniform or consistent followup

Reference – Dakeishi, M. et al., 2006, Long term consequences of arsenic poisoning during infancy due to contaminated milk powder. Environmental Health 5:31, published online 10/31/06.

Perinatal exposure to inorganic arsenic

Fetal loss and infant death – Effects of arsenic exposure on fetal and infant survival were evaluated in a Bangladeshi population. In a cohort of 29,134 pregnancies from 1991-2000, use of drinking water containing > 50 ppb of inorganic arsenic significantly increased risks of fetal loss (RR=1.14, 95% CI 1.04-1.25) and infant death (RR=1.07, 95% CI 1.03-1.32). A significant dose-response relation was found between arsenic exposure and risk of infant death.

Comment – Large sample size strengthens confidence in findings.

Reference – Rahman, A., et al., 2007, Association of arsenic exposure during pregnancy with fetal loss and infant death: A cohort study in Bangladesh. Am. J. Epidemiol. 165: 1389.

Perinatal exposure to inorganic arsenic

Lung cancer and bronchiectasis – Antofagasta, Chile, used drinking water with ~ 800 ppb of arsenic from 1958 to 1971. Hence, cohorts can be identified that were born just before (1950-57) or during (1958-71) the period of high arsenic levels in drinking water. For the just before cohort, SMRs for lung cancer was 7 and for bronchiectasis was 12.4. For the during cohort, the corresponding SMRs were 6.1 and 43.6.

Comment – Essentially an ecological study design

Reference – Smith A.H. et al., 2006, Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. Environmental Health Perspectives 114:1293.

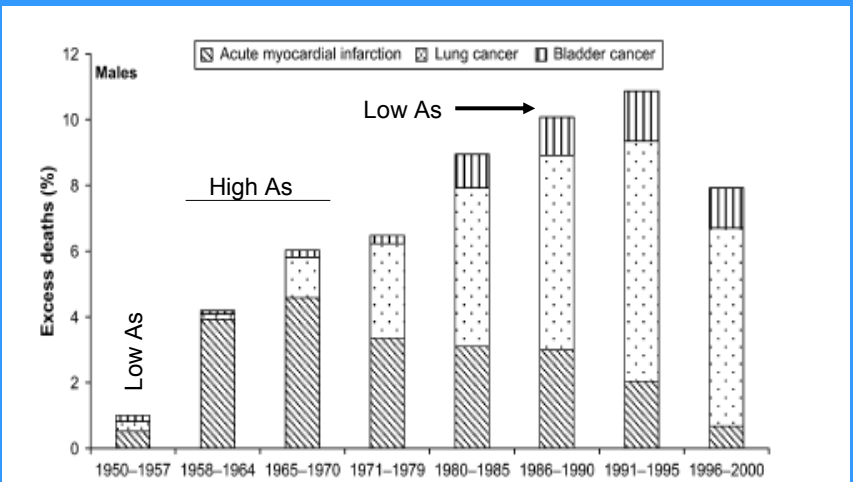
Perinatal exposure to inorganic arsenic

Acute myocardial infarction (AMI) mortality – In the Antofagasta, Chile, cohort that used drinking water with ~ 800 ppb of arsenic. Highest AMI mortality rate ratios (3.23) found in men born during the highest exposure period (1958-1970). AMI mortality was the predominant cause of excess deaths during and immediately after the high exposure period. Then AMI mortality declined and lung and urinary bladder cancer rates rose.

Comment – Suggests an effect of early life exposure to arsenic on cardiovascular disease

Reference – Yuan, Y. et al., 2006, Acute myocardial infarction mortality in comparison with lung and bladder cancer mortality in arsenic-exposed region II in Chile from 1950 to 2000. Am. J. Epidemiol. Published online Sept 17, 2007.

Effects in Chilean population suggest strong responses to exposure in early life



Yuan et. al., 2007

Perinatal exposure to inorganic arsenic

Immune function in children – Assess immune function in six to 10 year old children from Zimapan, Mexico, who consumed drinking water containing inorganic arsenic. Increased urinary arsenic concentration was associated with reduced PHA-stimulated mitogenesis in peripheral blood mononuclear cells, altered CD4/CD8 cell ratios, and reduced IL-2 secretion. Suggests chronic exposure to inorganic arsenic in childhood is immunosuppressive.

Comment – Difficulty in assessing significance of changes in immunocyte functions evaluated in *in vitro* assays.

Reference – Soto-Pena, G.A., et al., 2006, Assessment of lymphocyte subpopulations and cytokine secretion in children exposed to arsenic. FASEB J. 20, 779.

Perinatal exposure to inorganic arsenic

Intellectual Function – In Bangladeshi population find that arsenic in drinking water was associated in a concentration-dependent manner with reduced intellectual function. This effect persists after adjusting for covariates.

Comment – Standardized tests used have not been validated in this population, small sample size (n=201), possible effect of manganese in water supply requires further evaluation.

Reference – Wasserman, G.A., et al., 2004, Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environmental Health Perspectives 112:1329.

Effects of early life exposure

- Inorganic arsenic is a transplacental carcinogen in the mouse
- Fetal wastage is associated with in utero exposure in humans
- Impaired neurodevelopment is associated with early life exposure
- Evidence that in utero/early life exposure increases risks of cardiovascular disease and cancer

Research needs and future directions

Susceptibility and risk assessment

- Need to identify increased risk of disease or impairment that can be associated with an identifiable modifier of susceptibility (genotype – phenotype connection)
- Determine the frequency of occurrence of the modifier in populations of interest

Developing organisms and risk assessment

- Need to determine the range of effects that can be attributed to arsenic exposure in early life
- Animal models may be helpful in focusing research in human populations
- Need to assess exposure in fetus, newborn, and child to determine dose metric for evaluating effects

Contributors

EPA - NHEERL
B. Adair
M. F. Hughes
D. Wolf

EPA - NERL
J. Creed
M. Fricke (ORNL)
S. Conklin (ORNL)

NPI-Mexico
L. M. Del Razo

UNC
W. Xing
M. Styblo
Z. Drobna
V. Devesa
A. Hernandez-Zavala

TIGR/JCVI
J. Li

IAC-Prague
T. Matousek
J. Dedina

Questions, Answers, and Comments

Q. Mark Johnson: Does the arsenic methyltransferase have other substrates besides arsenic?

A. David Thomas: It doesn't methylate other metalloids like selenium. It doesn't methylate any other metals.

Q. Mark Johnson: Is it retained in evolution?

A. David Thomas: It can be traced back 500 million years ago in sea urchins. It is almost identical to the arsenic methyltransferase today.

Q. Elizabeth Doyle: Is the polymorphism that is conserved worldwide?

A. David Thomas: It is in about 10 percent of the population. We looked at African Americans, North American Indians, and South American populations, and they all came out at about that. They all were about 8 to 10 percent.

Arsenic Mode of Action and Developing a BBDR Model

Douglas Wolf
U.S. Environmental Protection Agency, National Health and
Environmental Effects Research Laboratory
(919) 541-4137
wolf.doug@epa.gov

Visuals follow. Please contact the speaker for more information.

The current USEPA cancer risk assessment for inorganic arsenic is based on a linear extrapolation of the epidemiological data from exposed populations in Taiwan. However, proposed key events in the mode of action (MoA) for arsenic-induced cancer (which may include altered DNA methylation, altered DNA repair, and induced reactive oxygen species) suggest the possibility of a nonlinear response at low doses. We are developing a biologically based dose response (BBDR) model for arsenic carcinogenicity to reduce uncertainty in estimates of low dose risk utilizing data on the mode of action and its human relevance. The Human Relevance Framework (HRF) and Mode-of-Action analysis is used to assess the relevance of an increased frequency of neoplastic lesions in rodents identified in carcinogenicity studies. This approach provides a framework for assessing possible cancer risks from exposures to pollutants or other agents in the environment. The goal is to make greater use of the scientific understanding of the process of carcinogenesis. The process includes analyzing all available information, identifying the key events in the cancer processes from exposure to adverse health consequence, describing the mode(s) of action and its biological plausibility in humans, considering differential susceptibility to subpopulations, and finally characterizing the risk to humans based on the weight of scientific evidence. The level of biological details that will be incorporated into the model will be determined largely by the availability of data. This model development effort will increase our understanding of how biological factors determine the shape of the dose-response curves for arsenic-induced cancer. [This abstract does not represent EPA opinion or policy]

Arsenic Mode of Action and Developing a Biologically Based Dose Response Model

Douglas C Wolf, D.V.M., Ph.D., Fellow IATP, ATS

Rory B Conolly, D.Sc.
Stephen W. Edwards, Ph.D.
Yuchao (Maggie) Zhao, Ph.D.

National Health and Environmental Effects Research Laboratory
National Center for Computational Toxicology
Office of Research and Development
U. S. Environmental Protection Agency

Contact: wolf.doug@epa.gov 1/9/2008

Cancer Guidelines 2005

Set forth recommended principles and procedures for assessing cancer risks.

Inform EPA decision makers and the public about these procedures.

Are meant to be a dynamic and flexible document.

Will be updated by additional supplemental guidance as experience and scientific understanding evolve.

http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283

EPA United States Environmental Protection Agency

Mode of Action

Mode of Action concept developed to provide a practical alternative to the complexity of the full mechanism of action

Mode of Action analysis identifies one of more key events that are rate limiting biological response that lead to the adverse health effect (ie cancer) or are bioindicators of such a response.

Keep Mode of Action description as simple as possible.

- Focus on key events that determine dose-response and time course behaviors

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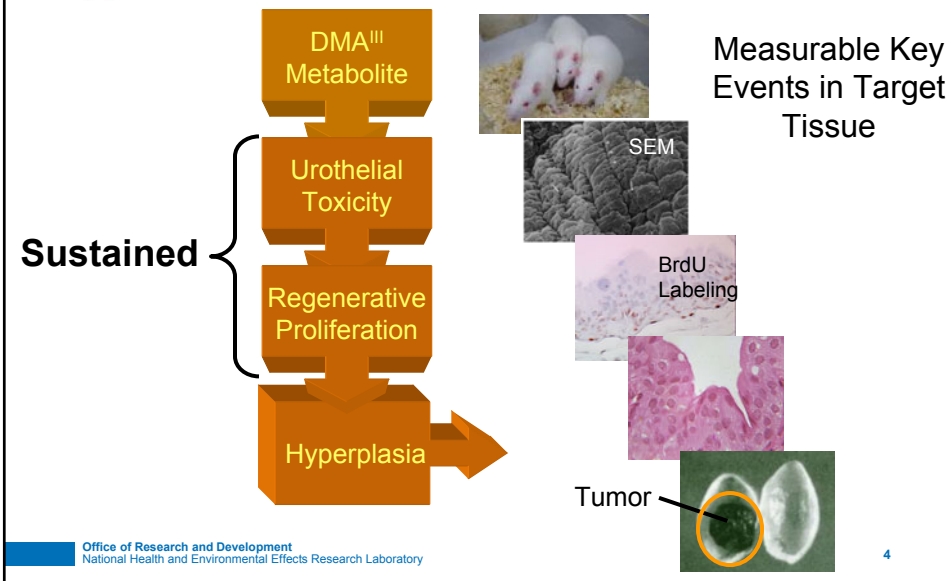
Describe the Animal Mode of Action

Mode of Action: Identify Key Events



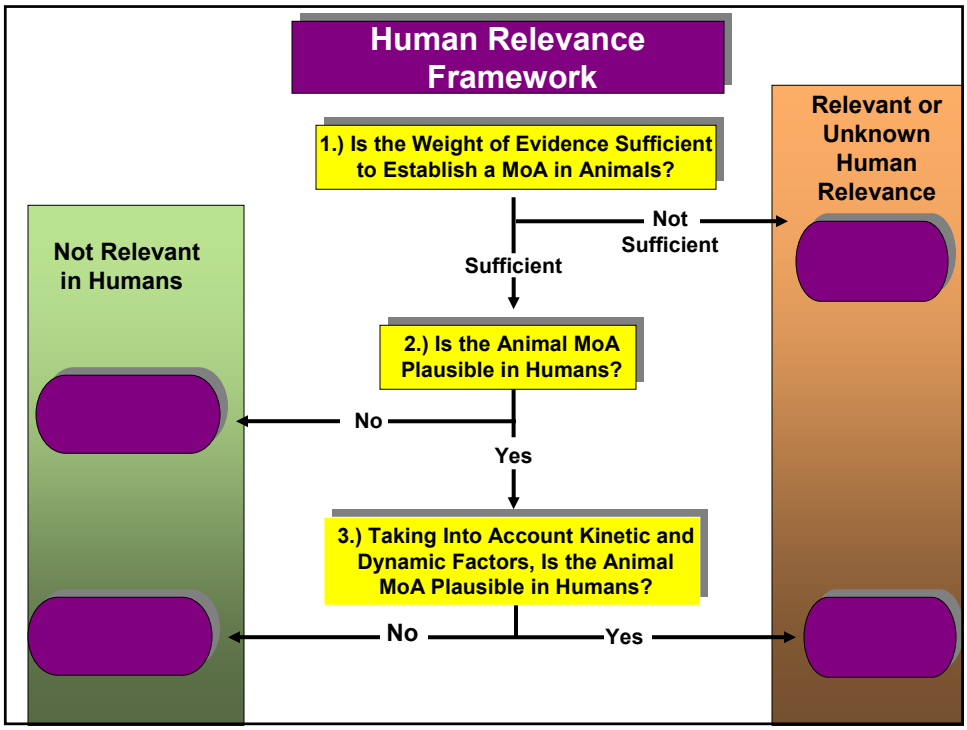
Biological Plausibility in Humans

Concordance Analysis of Key Events

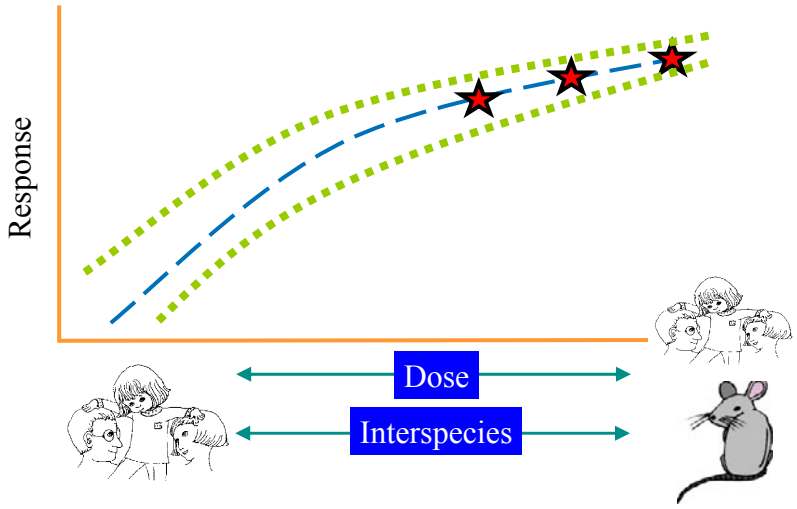
Key Event	Rodents	Humans
Presence of metabolite	Yes	Yes
Persistent cytotoxicity	Yes	Possible
Persistent regenerative proliferation hyperplasia	Yes	Possible
Tumors	Yes	Possible

Concordance analysis of key events is for the MOA and not necessarily chemical specific

Chemical specific & generic information relevant to the carcinogenic process is useful information



Goal: Accurate extrapolation with minimal uncertainty



Accuracy and Uncertainty

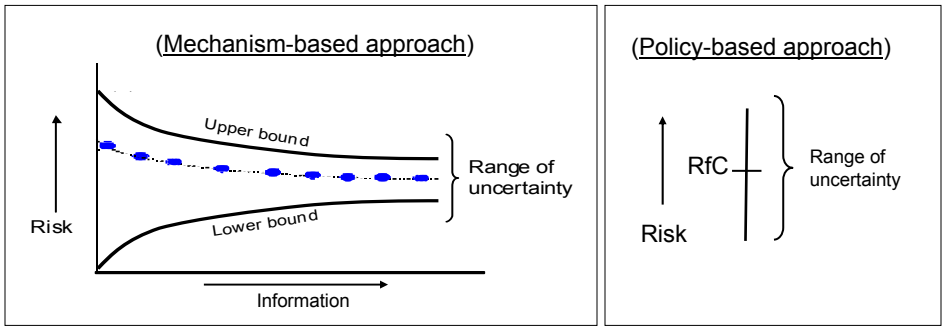
Accuracy

- Distance between actual and predicted risks is small

Uncertainty

- Range of risks in which actual risk may lie
- Need for quantification

The risk prediction with the least uncertainty is preferable



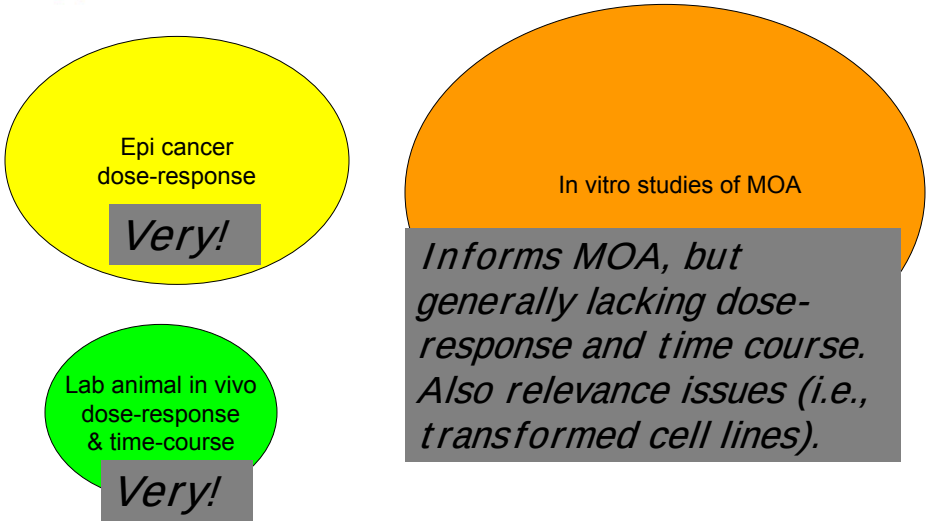
Mode of Action data needs to support Biologically Based Dose Response modeling

Dose-response and time course data for key events that are plausibly linked to each other.

Preferably *in vivo*

In vitro studies should address extrapolation to *in vivo*

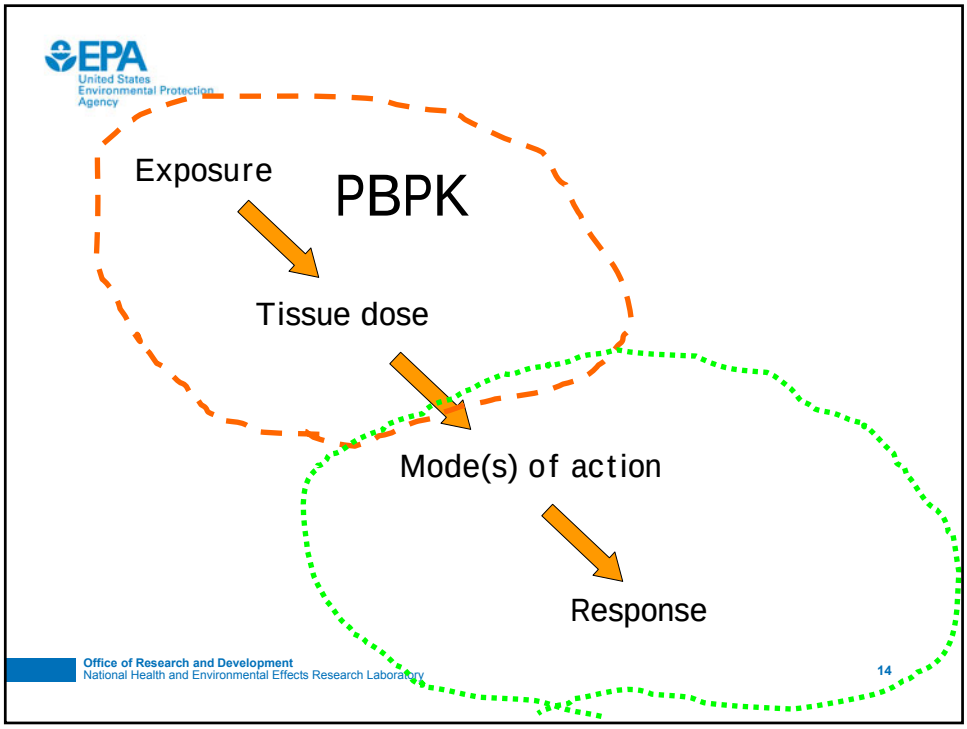
Relevance to model development

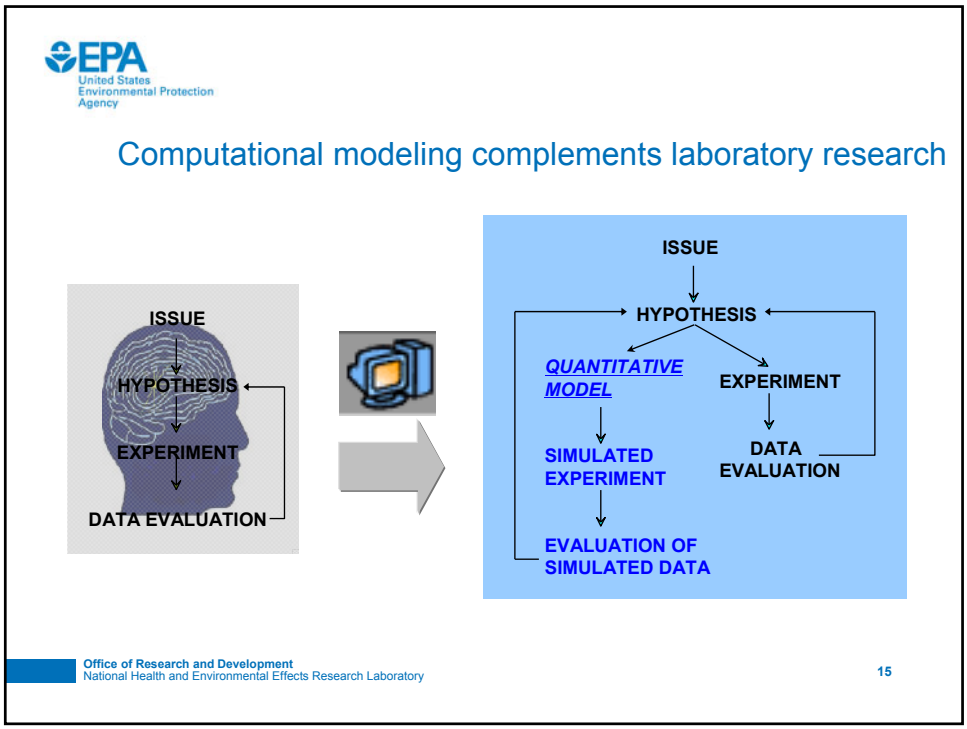


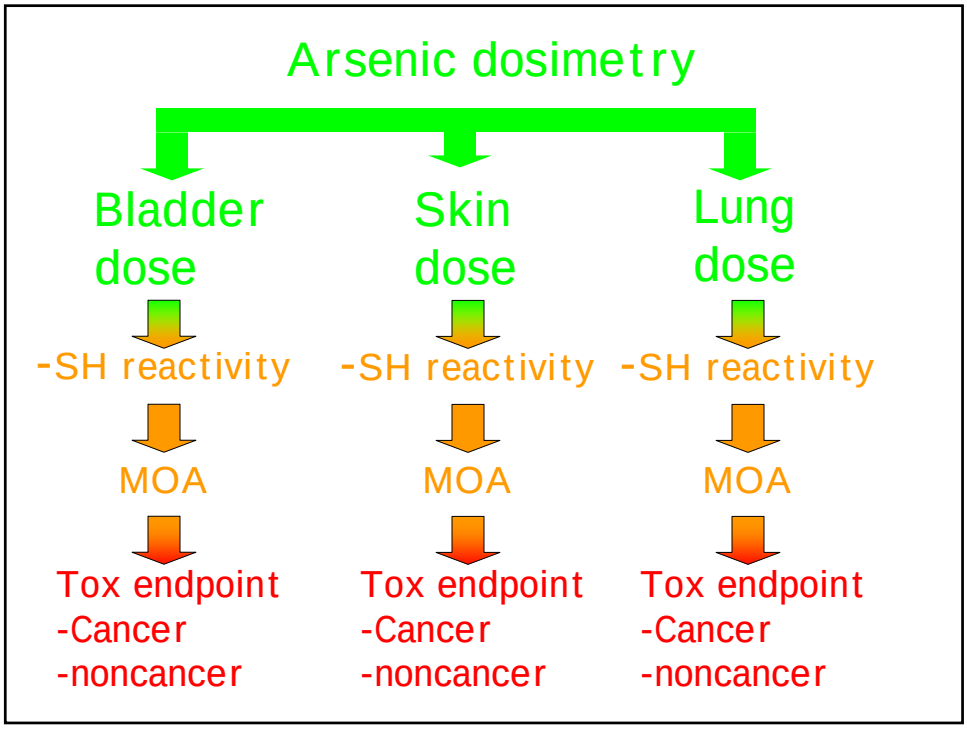
Computational models of biological systems

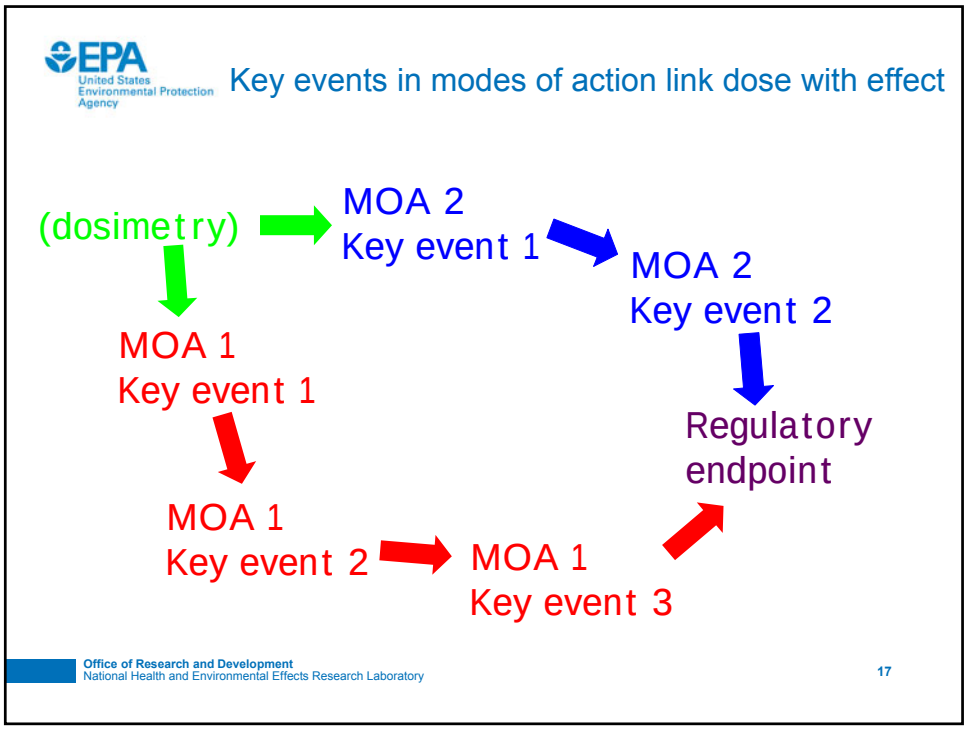
Biology determines
- The shape of the dose-response curve
- The qualitative and quantitative aspects of interspecies extrapolation

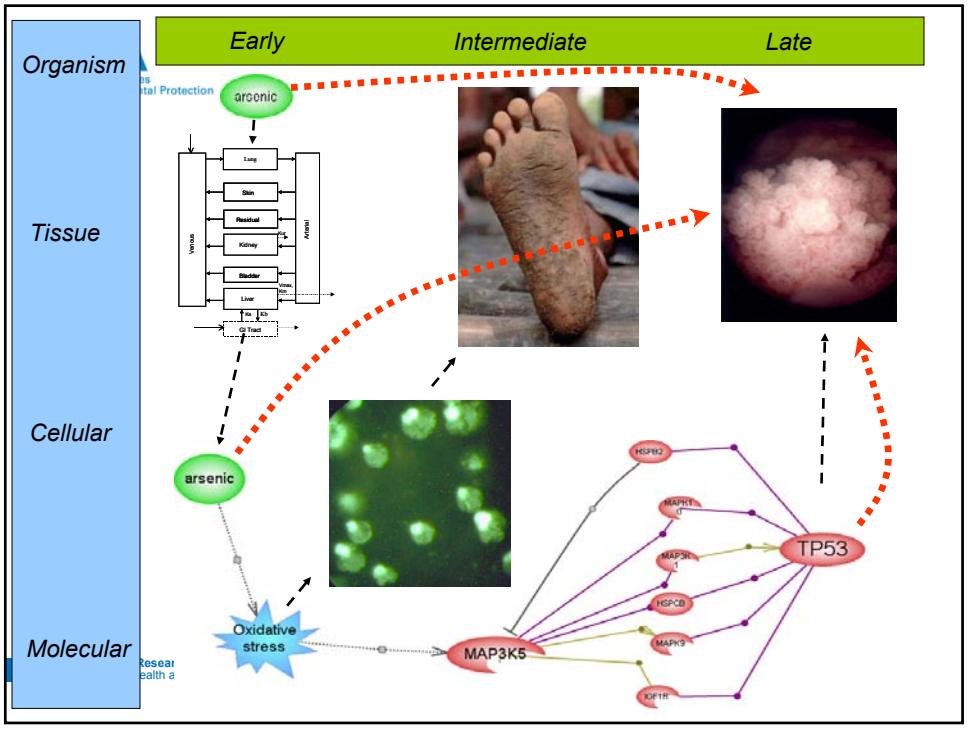
Biological structure and function can be
- described mathematically
- encoded in computer programs
- simulated


EPA
United States
Environmental Protection
Agency
Exposure
PBPK
Tissue dose
Mode(s) of action
Response
Office of Research and Development
National Health and Environmental Effects Research Laboratory
14


EPA
United States
Environmental Protection
Agency
Computational modeling complements laboratory research
ISSUE
HYPOTHESIS
EXPERIMENT
DATA EVALUATION
ISSUE
HYPOTHESIS
QUANTITATIVE MODEL
EXPERIMENT
SIMULATED EXPERIMENT
DATA EVALUATION
EVALUATION OF SIMULATED DATA
Office of Research and Development
National Health and Environmental Effects Research Laboratory
15


Arsenic dosimetry
Bladder dose
Skin dose
Lung dose
-SH reactivity
-SH reactivity
-SH reactivity
MOA
MOA
MOA
Tox endpoint
-Cancer
-noncancer
Tox endpoint
-Cancer
-noncancer
Tox endpoint
-Cancer
-noncancer


EPA
United States Environmental Protection Agency
Key events in modes of action link dose with effect
(dosimetry)
MOA 2
Key event 1
MOA 2
Key event 2
Regulatory endpoint
MOA 1
Key event 1
MOA 1
Key event 2
MOA 1
Key event 3
Office of Research and Development
National Health and Environmental Effects Research Laboratory
17



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Priority Research Considerations

Describe the key events in the continuum from arsenic exposure to development of adverse health effects.

PBPK model that describes the time-dependent tissue- and cellular-level concentrations of the arsenical species that elicit changes in cellular structure and function.

Data to develop a quantitative biologically-based dose-response (BBDR) model

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Impact

Establish exposure concentrations that are scientifically defensible and based on the relevant adverse health effects from long-term low dose exposure.

Predict changes in dynamics for susceptible populations.

Questions, Answers, and Comments

Q. Elizabeth Doyle: When will you be done?

A. Doug Wolf: It's part of our multiyear plan. We plan to have it out by fiscal year 2010 and have the application BBDR 1.0 out by fiscal year 2011. We have actually had intense meetings the past 2 days in concert with various program offices about the path forward. We have a defined research plan, and we will be off and running at the first of the year.

Q. Elizabeth Doyle: How do you see this being applied to other chemicals?

A. Doug Wolf: One advantage is that once you've done one, you know something about how to do it. Some of our team worked on formaldehyde. I used to be at CIIT Centers for Health Research, where we developed an air flow model for the nose that took 10 years to describe in the rat, 1 year to describe in the monkey, and a month to describe in the human. Once you do it once, it subsequently gets faster. We know what data are needed, and we can use that information to design research programs in the future.

Q. Mark Johnson: Genetic instability is the first key event mode of action. It looks like different mechanisms achieve the same endpoint.

A. Doug Wolf: Genetic instability is part of the cancer process. Is something impacting the cell, or is the cell developing instability in the genome? Is it spontaneous or direct or indirect? This is described in the analysis. Are changes in methylation an important key event or an incidental event? We look at the effects that are occurring at the cellular and molecular levels and whether they occur at high or low doses. Dr. Thomas talked about in utero exposures and epigenetic changes. Enhanced susceptibility can be figured in later in modeling. Some results may tell us about DNA damage, and some results may show normal changes that occur leading to carcinogenesis. We need to describe those as well.

Q. Ambika Bathija: We have one last item for today—the state's hot topics. Can we meet at 8:00 a.m. tomorrow to discuss it? Let's have a poll. Who wants to come in at 8:00 a.m. tomorrow?

A. Audience: *The majority of people raised their hands.*

C. Ambika Bathija: Let's meet tomorrow at 8:00 a.m.